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*Review Article*

# Etiological Role of Environmental Toxicants in Polycystic Ovarian Syndrome

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## ABSTRACT

Polycystic ovary syndrome (PCOS) is termed as the most common and complex reproductive and metabolic disorder, marked by increased androgen levels, irregularities in the menstrual cycle, and/ or small cysts on either or both the ovaries. About4%–8% women in the age of child-bearing are most commonly affected by PCOS, as per the prevalence estimates of NIH/NICHD criteria. Obesity, amenorrhea or oligomenorrhea, hirsutism, and most frequently infertility are the clinical manifestations included. Type-1 Diabetes Mellitus, Type-2 Diabetes Mellitus, and gestational Diabetes Mellitus are the risk factors for adults with PCOS. Both environmental and genetic changes give rise to PCOS. Endocrine disrupting chemicals (EDCs) intrude with the action of hormones which further disturbs homeostasis, resulting in revamping of the physiology during the whole lifetime of an individual, from fetal development to adulthood. Chemicals recognized as endocrine disruptors are diethylstilbestrol, polychlorinated biphenyls (PCBs), dioxin and its analogues, *Dichlorodiphenyltrichloroethane (DDT)*, and few other pesticides. Lifestyle factors associated with PCOS are: Increased body mass index, nutrition and diet as well as health care utilization. Modifying those behaviors can mitigate or prevent excess disease in such populations and should be taken into consideration in order to reduce human exposure to protect current and future generations from their adverse health effects, which will ultimately prevent or alleviate the severe metabolic sequelae of PCOS.

***Keywords:*** PCOS, Endocrine disrupting chemicals (EDC's), Exposure, Environmental toxins, Lifestyle.

## INTRODUCTION

One of the most common and complex reproductive and metabolic disorder, marked by elevated androgen levels, menstrual irregularities, and/or small cysts on either or both the ovaries is termed as Polycystic ovary syndrome (PCOS) [1] as reported in modern medical literature by Stein and Leventhal in 1935. [2] The underlying pathophysiology and variable phenotypes, of this condition is not yet completely understood. [3]

About 4%–8% women of reproductive age are most commonly affected by PCOS, as per the prevalence estimates of NIH/NICHD criteria. Obesity, amenorrhea or oligomenorrhea, hirsutism, and most frequently infertility are the clinical manifestations included. Type-1 Diabetes Mellitus, Type-2 Diabetes Mellitus, and gestational Diabetes Mellitus are the risk factors for adults with PCOS. [4]

In vitro, overexpression of a protein resulted in reproduction of PCOS

phenotype, which is differentially expressed in both normal and carcinogenic development cells, which is identified by genome-wide association screening. Commonly associated metabolic disturbances such as obesity, insulin resistance, dyslipidemia, and hypertension may serve as clues in the diagnosis of PCOS. [5]

In about half of PCOS' patients, either obesity related or intrinsic insulin resistance related or both obesity related and intrinsic insulin resistance related metabolic syndrome occurs whereas tissue-selective effects are observed in compensatory hyperinsulinism, which may result in the aggravation of hyperandrogenism. By the interlikage of diverse environmental and genetic factors, a complex trait in PCOS is observed. The genetic studies of PCOS have been outlined by phenotypic confusion. Although several gene loci including CYP11A gene, the insulin gene, a region nearby insulin receptor and the follistatin gene are expected as PCOS genes, the evidence approving linkage is not overwhelming. [6]

Polycystic ovarian morphology (PCOM), high levels of androgens in females (hyperandrogenemia), insulin secretory defects, and insulin resistance are the heritable factors involved, whereas environmental factors includes poor fetal growth and prenatal androgen exposure, acquired obesity is one of the major postnatal factor. The association of a various pathways and lack of common thread provides a clear evidence of the diversity of the syndrome and its multifactorial nature. [7]

Both genetic and environmental changes contribute to PCOS. Obesity, provoked by poor dietary choices and physical inactivity, worsens PCOS in prone individuals. The role of additional environmental modifiers such as environmental toxins or infectious agents is hypothetical. [8]

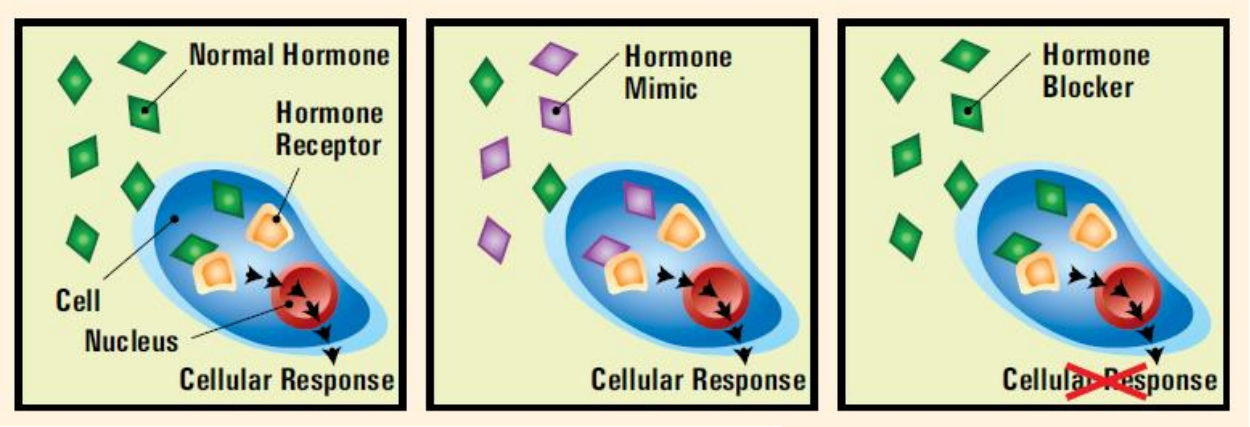
Despite evidence from human studies is inadequate regarding potential prenatal environmental factors, there is further documentation that postnatal exposure to environmental risk factors are associated to PCOS. Unhealthy lifestyle factors, including obesity and lack of physical activity have been suggested as potential environmental risk factors associated with the metabolic conditions related to PCOS. [9] As diverseness of its features is observed within ethnic races, families and geographic location indicates that environment and lifestyle are of prime value. [10]

Hence in the present review we therefore aim to have a look on the ongoing research on environmental toxins for this syndrome in the pathogenesis of PCOS so as to reduce human exposure to protect current and upcoming generations from their unfavourable health effects.

**Environmental factors: The throwbacks of modernization**

Endocrine disrupting chemicals (EDCs) intrude with the action of hormones, disturb homeostasis, and may revamp physiology during the whole lifetime of an individual, from fetal development to adulthood. [11] In order to gain a clear image of the etiology of hormone-related diseases, understanding how EDCs affect physiological processes and initiate pathophysiology is necessary. At environmentally relevant doses, some EDC's attach to hormone receptors and act as either agonists or antagonists, thus enhancing, dampening, or blocking the action of hormones. They also modify the number of hormone receptors in distinct cell types and the concentration of circulating hormones. [12,13]

These effects generate alternative phenotypes, depending on time and exposure of the dose, which may result in increased disease susceptibility. If exposure changes hormone actions during ontogenesis, the effects are generally permanent and can affect organ growth and activity. Furthermore, these effects could have lifetime consequences that are both complex and difficult to predict. [14]




*Pathophysiology describing an endocrine disruptor which, when taken up by the body, can increase or decrease normal levels of the hormones (left), imitate the body's natural hormones (middle), or make changes in the natural generation of hormones (right).;* ***Source:*** *Image from National Institute of Health Sciences (NIH) article on Endocrine Disruptors.*

There are tremendous uncertainties in estimating what might be a safe level of exposure to hazardous man-made chemicals, especially when they retain in the body for longer duration. This is in due as a result of a lack of exposure data and toxicity data for an ample majority of chemicals people are exposed to. It is challenging to propose that exposure to a certain chemical at a certain concentration will cause a peculiar adverse effect. The optimum way to counter this continuing chemical contamination and the menace to future generations is to avoid the manufacture and use of chemicals that are found in higher concentration in body fluids like blood and breast milk. [15]

**Endocrine Disruptors:**

Among the environmental pollutants suggested to be linked to such hormonal disorders are the polychlorinated aromatic hydrocarbons (PHAH), a group of ubiquitous environmental contaminants which include dibenzofurans (PCDFs), polychlorinated di benzoicp-dioxins (PCDDs), and biphenyls (PCBs). [16]

A broad and varied range of substances are thought to induce endocrine disruption including bisphenol A, phthalates, polybrominated flame retardants, some organochlorines, perfluorinated substances, alkylphenols, solvents, polycyclic aromatic hydrocarbons, and some domestic products including some sanitation products, air fresheners, cosmetics, hair dyes, and sunscreens. Along with the above mentioned some metals also mimicked endocrine-disrupting properties. [17]

Known endocrine disrupting chemicals include diethylstilbestrol, polychlorinated biphenyls (PCBs), dioxin and its analogues, DDT, and few other pesticides.

**Bisphenol A(BPA)**

BPA is an elevated-concentration organic synthetic chemical, observed in plastic and the epoxy resins which are used mostly in food packaging containers that store food and beverages, such as water bottles. Thereby, food is believed to be a major source of BPA intake. [18] Wide prevailing exposure to BPA has provoked the search for alternatives for use of BPA in polycarbonate baby bottles [19] and for food companies to remove BPA from canned foods. Lakind and Birnbaum [20] discusses the problems with coated cans for food by focusing on caution that alternate chemicals for BPA canned foods which could pose issues on their own. Lakind [21] in 2009 also reports Campbell's announcement of the removal of BPA in its soup products.

In 2008, the NTP center evaluated for risks of BPA inhuman reproduction and expressed that there are affects observed on

the brain, prostate gland of fetus and behavior in both infants and children. [22]

In women observed with PCOS, there was an association between environmental exposure to Bisphenol A (BPA) and decreased Antral follicle count, which suggested that BPA may affect human ovarian function. [23]

Another study indicated that BPA plays a main role in the pathophysiology of PCOS, by comparing 51 samples of PCOS-confirmed patients and the control group, which showed significantly elevated levels in PCOS group when compared to that of controls. This was further strengthened by the application of logistic regression analysis method which further conveyed BPA to be significantly associated with PCOS. [24]

In women diagnosed with PCOS and exposed to BPA, the quantity of BPA was significantly higher than those of healthy women exposed to BPA. This may be the reason for significant differences in the cholesterol, triglyceride, TSH levels and also in the LH:FSH ratio. These observations further confirm the potent role of BPA in the pathogenicity of PCOS. [25] In Caucasian PCOS patients, significantly higher levels of BPA were observed in PCOS-to-control ratio and study. This further point outs that serum BPA can be positively linked to PCOS diagnosed women and also involved in hyperandrogenism and the insulin-resistance of PCOS. [25]

**Phthalates**

Phthalates are a category of synthetic material derived from phthalic acid. These are termed based on the varying lengths of their alkyl chains, and act as environmental toxicants to humans who are exposed to it on a day-to-day basis. [27]

These are most commonly used as softener in polyvinyl chloride consumer, medical, and building products to confer flexibility, as excipients in dietary supplements and medications, and as solvents and matrices in products of personal care. As softeners, phthalates are available in regularly used products such as shower curtains, flooring, carpeting, roofing, packaging equipment, automotive parts, food and beverage packaging, and even in children's toys. Another form of phthalate is present in commonly used medical devices as such blood bags and intravenous bags, tubing, dialysis equipment, and also in the manufacture of disposable and surgical gloves. [28]

As solvents and matrices, phthalates are usually found in cosmetic and consumer products varying from perfumes and hairsprays to wood finishes and pesticides. Further, they are mostly used as lubricants, defoaming agents, and adhesives. [29] They are also present in the enteric coating of oral pills and also in dietary supplements ranging from probiotics to certain fish oils, in excipient form. [30,31] The presence of phthalate in some prescribed medication preparations of omeprazole, didanosine and theophylline, were found to be significantly high in those taking medications than those of reference population, as per the findings of Hernandez-Diaz et al., in 2009. Therefore, some medications can be a source of high exposure to some phthalates, thereby raising concern about potential human health risks with result to these exposures. [32]

Once consumed, phthalates rapidly metabolize in the stomach, liver, and blood stream by the action of esterases and lipases. Initially, phthalates induce toxicity by cleaving to its specific hydrolytic monoester where only one alkyl chain is remained on the phthalic acid. Depending on the size of the remaining monoester metabolite, the alkyl chain further undergoes oxidative metabolism and ultimately glucuronidation depending on species. [33,34]

EDCs can target follicles at various stages of folliculogenesis and exert ovarian toxicity. Chemicals can specifically target the primeval, preantral, antral, or primary population of follicles, or even target corpora lutea. Once a specific population is directed, the chemicals can provoke atresia and exhaust the follicles within that stage,

and can seize follicles under that stage, or can even promote accelerated development from that stage. Every single possible outcome can have adverse effects on non-reproductive health and/or fertility. EDCs that accelerate or deplete the growth of primordial follicles may result in permanent infertility which are mostly premature menopause induced, or premature ovarian failure induced. [35-38]

As per the analysis of Davis et al. 1994a, 1994b; and the analysis by Lovekamp and Davis in 2001, the experimental evidences suggests that DEHP inhibits the transcription of the enzyme aromatase and suppresses estradiol production in the ovaries of adult females. [39]

Due to their ubiquitous production, presence, and extensive use in the habitat, phthalates have the possibility to fix on the ovary at every stage of development and in adulthood. These detrimental effects can result in premature ovarian failure, decreased steroidogenesis and anovulation, infertility. [40-43]

Thus, disruptions of standard ovarian function by various different mechanisms, resulting in bothnon-reproductive and reproductive abnormalities are sequences of phthalate exposure. With reference to all these evidences, the current review suggests that both women and children, exposed to environmental phthalate and phenol are at high risk of developing hormonal abnormalities which might positively be related to social class.

A study was carried to assess the function of polychlorinated biphenyls (PCBs), environmental estrogens and phthalate esters (PEs) as probable environmental threat in decline of the semen parameters in men with infertility without any obvious etiology. The results revealed xenoestrogens as inversely proportional to absolute motile sperm count in infertile men and were remarkably lower than controls respectively. PEs and PCBs may be significant to deteriorate the semen standards in men with infertility without any obvious etiology. [44]

53 males were evaluated and the potential role of PCBs as an environmental hazard in the retrogression of male fertility was observed. It was found that the sperm quality and quantity were remarkably lower in men with infertility when compared to that of controls. The maximum average PCB concentration was observed in the fish-eating urban habitants, followed by fish-eating rural habitants, non-fish-eating urban habitants and non-fish-eating rural habitants. The absolute motile sperm counts and the PCB concentration were contrary to each other and was significantly low than those of controls respectively. PCBs may be significant in the retrogression of sperm quality and quantity, as contaminated fish in diet was observed to be the main source of exposure. [45]

**Nickel and Chromium.**

Majority of the heavy metals inclusive of chromium, cadmium, and nickel are harmful industrial chemicals with a risk of exposure in both environmental and occupational settings that may lead to detrimental outcomes.

Both unique and similar genes and their pathways responded to oxidative stress induced by nickel, cadmium, chromium. Although all these three metals are observed to be genotoxic, the significance for damage of DNA in a study existed only with response to chromium. A hypoxic response was induced by nickel in addition to genes inducing response intricated in the structure of chromatin, perhaps by replacement of iron in main proteins. Cadmium markedly unsettles the genes linked with endoplasmic reticulum stress and invoke the response of unfolded protein which results in apoptosis. With these studies, a first gene expression for the comparative analysis of chromium, nickel, and cadmium in the H4-II-E-C3 cell type have been completed. [46] These findings indicate a relationship between PCOS and increased copper concentration. [47]

High serum copper and nickel with low Zinc levels are associated with PCOS in our study. Chronic copper overload may have exaggerated insulin resistance that is associated with PCOS and deficiency of Zinc cause oxidative stress to act on PCOS by affecting the hormone levels; these results provide indication to observe the mechanism of PCOS and counsel for detail treatments in PCOS patients in clinically conducted trials associated to antioxidant supplementing in PCOS. Additional studies are needed for the evaluation of the effects copper and Zinc in PCOS' patients affiliated to insulin resistance and oxidative stress. [47]

Further abnormal features were discovered in the spermatic fluid of the workers exposed. Seminal fluid abnormalities were correlated with the total of years susceptible to welding fumes, holding chromium and nickel. [49] Serum Malondialdehyde (MDA) levels, an Oxidative Stress (OS) attribute, were discovered to be certainly correlated with Micronucleus (MN) in PCOS' patients and not the healthy. [50] Additionally, DNA copy numbers of the mitochondria was unfavorably correlated with indicators as such triglyceride levels, waist circumference, and insulin resistance and were positively correlated with globulin level binding sex hormones. [51] Remarkable correlations were observed among DNA strand breakage and free testosterone including damage to DNA induced by $H_2O_2$. [52]

As mentioned above, there are deep-seated interactions between and oxidative stress, obesity and insulin resistance. It gives the impression that the oxidative stress which is altered in PCOS, has enhanced the gene instability and also the risk of DNA mutation which may probably contribute in the gynecological cancers' pathogenesis.

**Lead (Pb)**

Lead is the common element available in low quantity on the Earth's crust. It is used widely in industries, especially in products like paint, piping, materials of construction, and batteries. It causes many health problems as such toxicity of the kidneys, liver, nervous system and the hematopoietic system. IARC classified the inorganic lead products to be likely carcinogenic to humans as found with the risks of carcinogenicity. [53]

Major symptoms in adults include stomachache, headache, abnormal sexual function, and decreased sensation in limbs, loss of memory, renal failure, and the early phase symptoms which are non-specific like, decrease in appetite, depression, intermittent stomachache, diarrhea, constipation, and nausea may be manifested. [54]

Lead, including multitude environmental toxic agents may cause infertility and other alterations. This toxic environmental pollutant is widely spread and affects both female and male reproductive systems of humans [55] and in the experimental animals. [56] Most of the common effects reported in women includes increase in the time to conceive, infertility, miscarriage, pregnancy associated hypertension, preeclampsia, premature delivery, [57-59] hypermenorrhea, abnormal and prolonged menstruations, polymenorrhea, and an increase in the prevalence of spontaneous abortions. [60] In fact, as early as in 1965, Gilfillan [61] suggested that the declining birth rate in Rome's ruling class, which may have been at the root of the empire's dissolution, was a consequence of exposure to lead in food and wine.

It has been demonstrated that lead and Cadmium exert endocrine disrupting properties. The possible role of these metals in endometriosis is not yet known. In 119 patients, urinary excretion of cadmium (CdU), and concentration of lead in blood (PbB) and cadmium (CdB) was compared with endometriosis of peritoneum and or deep endometrial nodules of 25 controls and the rectovaginal septum. Among the groups, there was no difference among the average levels of cadmium in urine and blood. Low amount of PbB was observed in women affected with endometrial diseases than that

of controls. Their data could not support the role of cadmium in the initiation or development of endometriotic condition but suggested a possible lead relationship. [62]

Lead (Pb) is a toxic metal found ubiquitously. Workers of secondary Pb recovery unit are susceptible to occupational lead exposure. The exposed workers were observed with increased levels of damage to DNA, which justified the genotoxic effects of Pb in exposed humans. [63]

**Pesticides**

The hormonal function in females may be interfered by the use of some pesticides, leading to adverse effects on the system of reproduction by the disruption of hormonal balance which is necessary for its proper functioning. [64] Organochlorine pesticides which are used to eliminate insects are the persistent chemicals which and have now been banned in the U.S. These chemicals can bioaccumulate in fish, and diet is the main route of exposure for humans. [65]

Women with low levels of education, low levels of pesticide use safety awareness, [66] poor access to personal protective equipment, and limited training on proper use of pesticides might be at higher risk of exposure to pesticides and the resulting adverse health effects. As shown by Jors et al [67] lower levels of education are also associated with less knowledge of pesticides and with risky behavior when pesticides are being handled.

In the recent years, use of pesticides had been increasing, which resulted in the need for increased production of pesticides. However, some of the pesticides may also represent as danger to human health, especially by causing cancer. Genotoxicity tests perform an essential role in the cancer research and also in assessing the risk of potential carcinogens. The workers exposed had a significantly high mean than controls. Smokers had a significantly high mean than that of non-smokers. Covariance analysis conveyed that both smoking and occupational exposure had significantly high effects on the mean tail lengths, whereas gender and age had no effect on damage to DNA. It was suggested by their study that exposure to smoking and pesticides occupationally can result in damage to DNA which further confirms the susceptivity of the Comet assay. [68]

Two studies were carried out, which discovered a significant association among two different OCPs and endometriosis. [69]

**Drugs including Phyto-estrogens and Anti-epileptics:**

Drugs like digitoxin and digoxin have extensive clinical use to treat atrial dysrhythmias and heart failure. [70] In male patients taking cardiac glycosides for the cardiovascular diseases, decrease in the excitement and sexual desire are the primarily reported sexual problems. [71]

In the root to endometriosis, as multiple factors are involved, it has been indicated that exposure to dioxin may contribute to alteration in growth factors and immune response or imbalance of sex hormones. [72] This further alters tissue specific responses to hormones via transition of steroid receptor expression. [73]

Thereby, genetic background or cellular changes may predispose an exposure, resulting in infiltration and adherence of cells of the endometrium in the peritoneum. [74]

As PCOS is believed to be having a higher incidence in women with epilepsy and possibly bipolar disorder, multiple theories have been proposed to explain its higher prevalence and various disorders of reproductive system in these patient populations. This included the effects of itself the disease and of antiepileptic drugs, mainly valproate, which may directly lead to PCOS or indirectly result in the disorder by causing weight gain which further triggers insulin resistance, elevated testosterone levels, and other reproductive abnormalities. As there are no definite studies confirming the association between PCOS and anti-epileptics, medical practitioners need to be aware of the possibility in women of reproductive age to develop symptoms of PCOS, when treated

with antiepileptics. Therefore, the choice of antiepileptic drug for women with epilepsy/ bipolar disorder must be based on the most effective agent for the control of neurologic symptoms. [75]

As indicated by several studies, digitalis like drugs have the capability of attaching to the estrogen receptors, although it has lacking affinity than that of estrogen itself [76,77] It was also observed that occurrence of PCOS was also higher in patients with valproate compared to other anti-epileptics, untreated women with epilepsy, and the normal population. [78]

## CONCLUSION AND FUTURE RESEARCH

As assisted by immense data being derived from various scientific prototypes, broad exposure to toxins in environment as well as their part in PCOS' pathophysiology are assisted by strong recommendations and protective strategies. This initially includes exploration of environmental risk factors related to PCOS and their consequences, which have significant public health implications. Taking into consideration to the lifestyle factors found to be linked with PCOS including: Diet and nutrition, and suggested factors which include health care utilization and obesity. Modifying those behaviors can prevent or mitigate excess disease in such populations and should be taken for consideration in order to reduce human exposure to protect current and future generations from their adverse health effects, which eventually mitigate or prevent the severe metabolic consequences of PCOS.

**Authors Contribution**

All authors Dr. Roya Rozati and Dr. Sumaya Fatima contributed equally to this work. Dr. Roya Rozati along with Dr. Sumaya Fatima discussed and participated in the preparation of manuscript at all stages.

**Conflict of interest:** There are no conflicts of interest in this study.

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