

## Unfolding the impact of environmental factors on the evolution of Polycystic Ovarian Syndrome

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### Abstract

*In this review we highlight the detrimental effect of numerous environmental factors potentially implicated in the etiology, prevalence and inflection of polycystic ovarian syndrome (PCOS) in woman population. PCOS is a heterogeneous multifaceted disease of woman emanating infertility, abnormal fetal growth and irregular menstruation. Precisely, the leading environmental factors, we discuss, include oxidative stress, environmental toxins, lifestyle, nutrition and heavy metal elements causing the onset of PCOS. Research evidences explore that environmental toxins can potentially induce the oxidative stress through (reactive oxygen species) ROS generation, thereby disrupting the reproductive health system. Additionally the synergistic influence of certain dietary supplements and weight loss in obese women has also deliberated. The features of key nutritional factors in preventing or mitigating the growth of PCOS as well as its associated other metabolic disorder have been scrutinized. Finally, further research in these avenues is highly admirable since global scenario of PCOS is remarkably crucial pointer of socioeconomic, environmental and epigenetic factors that possibly leads to adverse health effects in future generations of the world.*

*Keywords: Environmental toxin, oxidative stress, Polycystic Ovarian Syndrome, reproductive health, lifestyle.*

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### Introduction

Polycystic ovary syndrome (PCOS) is a prevalent heterogeneous endocrineopathy with an occurrence of about 5.5– 19.9% [1]. This is a pivotal cause of certain complications in girls or women which include abnormal menstrual cycle and difficulty in conceiving. Also it can be symbolized by clinical or biochemical hyperandrogenism, and diverse morphological pattern of polycystic ovary [2]. In essence, PCOS is comprehensively considered to be the utmost origin of infertility in women which further impinges the phenotypic characteristics in women. The extrapolative approach that outlines the correlation between the severity of PCOS and cardiovascular risk associated with PCOS involves endothelial dysfunction (ED) and deformed cardiac structure [3]. Scrutiny of the cardiovascular risk factors such as hyperinsulinemia and unusual plasma lipids in PCOS women, indicates higher risk for developing CVD. These consequences signify PCOS in woman health proliferates far beyond the connotation for reproductive function [4, 5].

The spectrum of women having PCOS shows insulin resistance [6, 7] which is a leading cause of the development of obesity. PCOS is also defined by central adiposity [8] and the profile of metabolic perturbation is associated with several metabolic syndrome such as atherogenic dyslipidemia (high triglycerides and LDL-cholesterol levels in serum, low HDL-cholesterol levels) and impaired glucose

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tolerance leading to the development of Type 2 Diabetes [7]. Patients with PCOS are also defined by higher blood pressure values and increased thrombotic action and various cardiovascular as well as insulin resistance markers [8, 9]. The underlying concept of endocrinopathy is still ambiguous, nevertheless heterogeneity of its features implies that genetic factors as well as environmental factors and lifestyle are of precise and quantifiable in terms of clinical aspect [10].

This review primarily focuses insight into the possible impact of common environmental toxicant in the pathogenesis of PCOS. Also it will highlight the toxicological effect of several plasticizers including bisphenol A (BPA) or phthalates [11] and advanced glycation end products (AGEs) [12] majorly, creating progressive impact on human everyday health. In particular serious devotion should be paid to the current research on environmental risk factors of PCOS and spotlight some of the potential avenues for future perspectives.

### **Oxidative stress induced PCOS**

Oxidative stress (OS) occurs when there is an disequilibrium between the production of free radicals and and the body's ability to antagonize their detrimental effects through neutralization with antioxidants status in the body. A significant correlation between increased levels of reactive oxygen species (ROS) and insulin resistance were reported earlier [13]. The enhanced production of ROS influences the body's antioxidant defense system which in turn develops an adverse physiological environment in female. Generally oxidative stress in PCOS is of high concern irrespective of their lean body mass and metabolic abnormalities have been documented causing infertility among PCOS woman [14]. OS influences female reproductive system, it also governs cardiovascular system. Lipid peroxidation process revealing malonyldialdehyde (MDA) is recognized for OS while SOD, an antioxidant enzyme, offers a defensive mechanism of the body. Increased level of ROS leads to an increase in MDA levels. Lipid peroxidation induces ROS production which is a foremost cause of oxidative stress and damage [15].

### **Environmental Toxins**

#### **Endocrine disrupting chemicals**

Endocrine disrupting chemicals (EDCs) or endocrine disruptors are commonly defined as “exogenous substances or mixtures that alter function(s) of the endocrine system and subsequently show profound adverse effects in an intact entity or its progeny or (sub) populations [10]. Its potential interactive ability with hormonal receptors as agonists or antagonists triggers various metabolic molecular pathways. The unique molecular structure of EDCs assists the mimicking of steroid hormones resulting in its impaired synthesis, secretion, transport, metabolism and binding actions that are accountable for homeostasis, reproduction and developmental process. Over the last two decades, an alarming situation have arisen about the adverse effect of EDC on human health, therefore its safety measures have now become progressively more reinforced with new scientific and clinical resources. The affinity mechanism of the hormone receptors for the EDCs is still under a blurred vision and need to be addressed extensively through proper scientific evidence.

However, EDCs offer some distinct characteristic feature wherein long term exposure leads to serious health concerns in organism which have been noticed by toxicologists [11,12]. Moreover the timing of

EDC exposure during the lifespan appears to be crucial for the severity of biological effects, as younger organisms are more susceptible to EDCs' action. In children this effect is quite prominent and has higher exposures particularly through their hand to mouth activity. Typically EDCs metabolism and excretion is associated with liver and its enzyme uridinediphosphate-glucuronosyltransferase (UDP GT). Owing to its fascinating structure EDCs may encourage their bioaccumulation in the adipose tissue of humans. The traces of EDCs have been spotted also in biological fluids such as sera [14], urine [15], amniotic fluid [16] and breast milk. Importantly, the presence of EDCs in amniotic fluid and placenta is alarming threat as EDCs can further deteriorate the hormonal equilibrium, fertility status and fetal development of women [16].

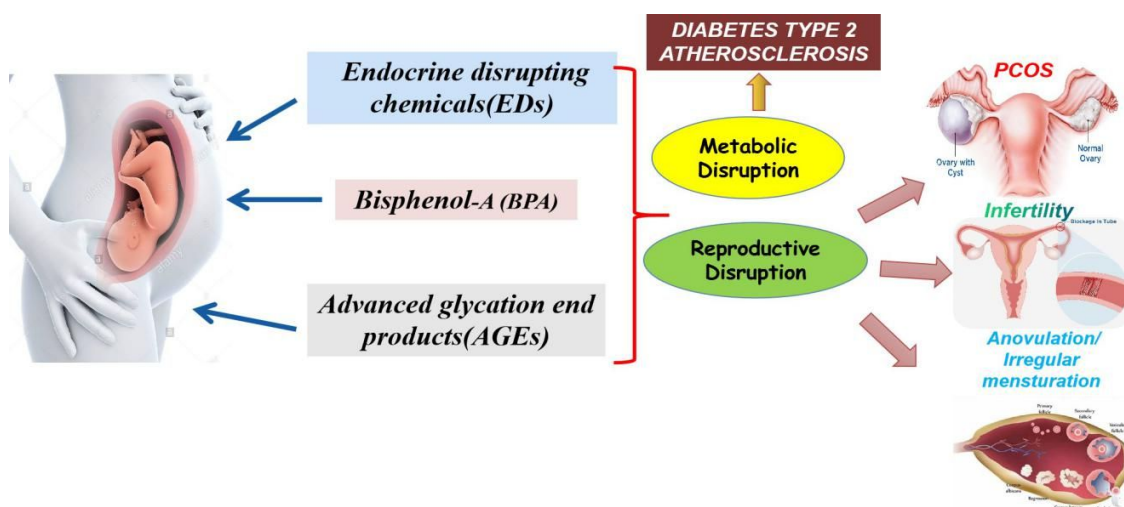
### **Bisphenol-A (BPA)**

The elevated concentrations of bisphenol-A (BPA) in women interfere with the regulation of hormone, possibly due to acquaintance to chemicals in the womb leading to the growth of polycystic ovarian syndrome [17]. Concurrently the higher BPA levels were also noticeably affiliated with androgen concentration which is playing a pivotal role in the incidence of PCOS in adolescent girls.

In addition glycation end-products and EDs also play pivotal role in the disruption hormonal homeostasis correlating with the impairment of reproductive functions. This is possibly responsible for various metabolic abnormalities such as insulin resistance, obesity and hyperinsulinemia which are in turn responsible for development of PCOS consequences such as cardiovascular disease and type 2 diabetes [18]. Interestingly octylphenol induces a considerable effect on the insulin resistivity, index of PCOS. Many halogenated chemicals such as Polychlorinated biphenyl (PCBs), Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS), Polybrominated diphenyl ethers (PBDE), Perfluoroalkyl substances, especially perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are found prevalently in women having pregnancy [19]. The accumulation of these chemicals imposes risk to human health. Therefore, the persistent quantity of these chemicals in our daily food chain appears a serious concern leading to infertility, prematurity and abnormal fetal growth [20]

### **Advanced glycation end products (AGEs)**

AGEs, also termed as glycotoxins, are proinflammatory entity derived from nonenzymatic glycation and oxidation of proteins and lipid molecule [21]. Specially, elevated levels of AGEs trigger the activation of proinflammatory conditions and induce oxidative damage. Hence, the outcome of these findings involve the aging, diabetes, atherosclerosis, female fertility, and cancer progression [22].



**Figure 1: Schematic representation of the effect and outcomes of environmental toxins in woman reproductive system**

### **Lifestyles and dietary factors**

Lifestyle and dietary elements are considered as intrinsic factor for occurrence of PCOS. Obesity and body fat distribution through lifestyle alteration engender abnormal menstrual regulation and control various reproductive outcomes in woman. As per epidemiological survey conducted in Sweden, women aged group 14–31 years with oligomenorrhea showed increased body mass index (BMI) compared with control subjects, indicating the timing of the early screening of PCOS and its effective intervention [23].

Meanwhile increased visceral fat, as measured by magnetic resonance imaging scans, can also enhance the potential risk in woman through various metabolic abnormalities and different fat cell features. The current findings corroborate that sensible diet with carbohydrates, proteins, fats, and a high content of fiber, are favorable to improve overall health parameters in women with PCOS. Recently, lifestyle (diet and exercise) intervention was explored to maintain hormonal regulations and levels in PCOS. Therefore, lifestyle revitalizing program on behavioral & dietary management and versatile exercise interventions has been encouraged as an effective wheel for the risk reduction of certain metabolic syndrome, thus delivering an ameliorated infertility outcomes in patients with PCOS.

### **Impact of trace and heavy metals in PCOS**

Some trace metals are very crucial for performing various physiological functions in the living organisms. This essential trace metals including copper (Cu) zinc (Zn), manganese (Mn) and lead (Pb), Nickel (Ni) etc. The concentration of these metals may significantly executes for potential alteration of hormonal regulation within living organisms. Interestingly, trace metals such as copper and nickel possibly regulate reproductive hormonal activity concerned with PCOS and its allied disorders [24]. Several reports were published wherein the increased level of serum copper and nickel levels was noticed as compared with the reduced serum zinc in subjects with PCOS [25]. Further Sedighi et al. [26] manifested a comparative

study with sedentary lifestyle of woman and reported the association of dietary habit and physical activity with the manifestation of PCOS.

### **Conclusion and Future perspective**

In this review we contend the multifaceted feature of PCOS and the detrimental effects of environment towards its pathogenesis. This survey of the assessment of environmental risk factors related to PCOS and their serious concerns have vital public health implications. Several determining factors like healthy management of lifestyle, diet and nutritional supplements can lower the disease progression in population. Simultaneously early screening of PCOS in adolescence provides various interventions that eventually moderate the chronic metabolic PCOS in woman populations.

Summarily exploring environmental entities related to PCOS enables us to perceive the etiology and pathogenesis and epigenetic consequences of this adverse condition and also highlights the significant involvement of the trace metals towards negative health consequences. Hence schemes and strong endorsements should be arranged to diminish human exposure to defend near future from this progressively intensifying adverse health effects.

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