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UNFOLDING THE INFLUENCE OF ENVIRONMENTAL FACTORS ON THE MATURATION 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 with other metabolic disorder have 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.

KEY WORDS : Environmental toxin, Oxidative stress, Polycystic Ovarian Syndrome, Reproductive health, Lifestyle

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent heterogeneous endocrinopathy with an occurrence of about 5.5– 19.9% (Knochenhauer, 1998). This is a pivotal cause of certain complications in girls or woman which includes abnormal menstrual cycle and difficulty in conceiving. Also it can be symbolize by clinical or biochemical hyperandrogenism, and diverse morphological pattern of polycystic ovary (Wild, 1990). In essence, PCOS is comprehensively considered to be the utmost origin of infertility in women which further impinges the phenotypic characteristics in women from *in utero* life to till death. The extrapolative approach that outlines the correlation between the severity of PCOS and cardiovascular risk associated with PCOS involve endothelial dysfunction (ED) and deformed cardiac structure (McKittrick, 2002). Scrutinizing the cardiovascular risk factors such as hyperinsulinemia and unusual plasma lipids in PCOS women, indicate higher risk for developing CVD. These consequences signify PCOS in woman health proliferate far beyond the connotation for reproductive function (Allahabadia, 2008; Diamanti-Kandarakis, 2006).

The spectrum of women having PCOS shows insulin resistance (Diamanti-Kandarakis, 2012; Legro, 1999) which is a leading cause of the development of obesity. PCOS is also defined by central adiposity (Diamanti-Kandarakis, 2012) and the profile of metabolic perturbation is associated with several metabolic syndromes. Major concern of Type 2 diabetes associated with atherogenic dyslipidemia (high triglycerides and LDL-cholesterol levels in serum, low HDL-cholesterol levels)and impaired glucose tolerance (Legro, 1999). Patients with PCOS are also defined by higher blood

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pressure values and increased thrombotic action. Additionally various markers related to cardiovascular physiology as well as insulin resistivity significantly influences PCOS among patients (Diamanti-Kandarakis, 2011; Wild, 2010). The underlying concept of endocrinopathy is still ambiguous, nevertheless heterogeneity implies that genetic factors as well as environmental factors and lifestyle are of precise and quantifiable in terms of clinical aspect (Koch, 2015).

This review primarily 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 (Owens and Chaney, 2005) and advanced glycation end products (AGEs) (Vandenberg, 2012) 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 disequilibrium between the production of free radicals 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 (Murri, 2013). The enhanced production of ROS influences the body's antioxidant defense system which in turn develop an adverse physiological environment in female. Generally oxidative stress in PCOS is highly concern irrespective of their lean body mass and metabolic abnormalities has been accountable causing infertility among PCOS woman (Sabuncu, 2001). OS governs female reproductive system as well as cardiovascular system. Upon lipid peroxidation process malonyldialdehyde (MDA) is derived and recognized for OS while SOD, an antioxidant enzyme, offers as a defensive mechanism within body. Increased level of ROS leads to an increased level of MDA which is a foremost cause of oxidative stress and damage (Barkath Nisha Hyderali, 2015).

Environmental Toxins

Endocrine agitating chemicals

Endocrine disrupting/agitating chemicals (EDCs) or endocrine disruptors are commonly defined as ''exogenous substances or mixtures that amend functionality of the endocrine system and illustrate profound adverse effects in an intact entity or its progeny or (sub) populations (Koch CA 2015). 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 have been noticed by toxicologists (Owens, 2005; Vandenberg, 2012; Murri, 2013). Moreover the timing of EDC exposure during the lifespan critically employed the severity of biological effects, as adolescent organisms are more susceptible towards 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 uridine diphosphate-glucuronosyl transferase (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 (Sabuncu, 2001), urine (Barkath Nisha Hyderali, 2015), amnioticfluid (Palioura, 2013) 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 (Palioura, 2013).

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 (Akýn amd Kendirci, 2015). 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 are also play pivotal role in the disruption hormonal homeostasis correlating with the impairment of reproductive functions. This is possibly encumber to various metabolic abnormalities such as insulin resistance, obesity and hyperinsulinemia which in turn responsible for development of PCOS consequences such as cardiovascular disease and type 2 diabetes (Rutkowsk, 2016). Interestingly octylphenol induce 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 perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) found prevalently in women having pregnancy (Chaoba Kshetrimayum, 2019). The accumulation of these chemicals can also be source of exposure and impose 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 (Lam, 2014).

Advanced glycation end products (AGEs)

AGEs, termed as glycotoxins, are proinflammatory entity derived from nonenzymatic glycation and protein oxidation and lipid molecule (Monnier, 1990). Specially, elevated levels of AGEs trigger the activation of proinflammatory conditions and induce oxidative damage. Hence, the outcome of these finding involve the aging, diabetes, atherosclerosis, female fertility, and cancer progression (Palimeri, 2015).

Lifestyles and dietary factors

Lifestyle and dietary elements is considered as intrinsic factor to the 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 (Ollila, 2016).

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 and 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 execute for potential alteration of hormonal regulation within living organisms. Interestingly, trace metals such as copper and nickel possibly regulate reproductive hormonal activity concerned of PCOS and its allied disorders (Zheng, 2015). 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 (Taher, 2017). Further Sedighi *et al.* (2015) manifested a comparative study with sedentary lifestyle of woman and reported the association of dietary habit and physical activity with the manifestation of PCOS.

Prevalence of COVID-19 and PCOS

After COVID-19 pandemic outbreak profound

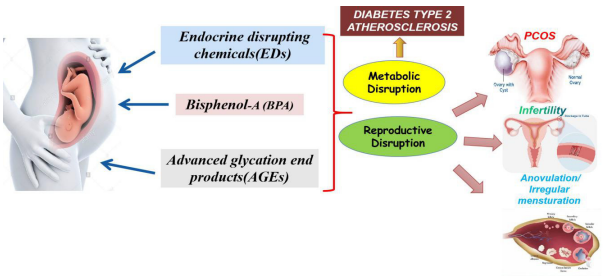

Fig. 1. Schematic representation of the effect and outcomes of environmental toxins in woman reproductive system

susceptibility to COVID-19 infection in women with PCOS is monitored. These research findings need to be acceptable to design the overall scheme of public health policy of understanding the COVID-19 scenario (Liu, 2015). PCOS is a pro-inflammatory state which is associated with various cardio-metabolic abnormalities. In PCOS several pro-inflammatory mediators involves such as C-reactive protein (hsCRP), tumour necrosis factor (TNF)-alpha, procalcitonin and interleukin-18 (IL-18) etc are identified in increased levels in circulation (Puder, 2005). Cytokines causing pro-inflammation are inculpated in adipose tissues dysfunction and inflammation which have been directly cultivated in the pathophysiology of insulin resistance. Severe COVID-19 infection demands oxygen therapy or admission to intensive care for intubation and ventilation further triggers the catastrophic acute respiratory distress syndrome (ARDS) with associated multi-organ failure and high mortality. The underlying pivotal cause lies on the low-grade pro-inflammatory predisposition derived from COVID-19 infection which in turn induce the obesity in PCOS woman (Montopoli, 2020).

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 include the healthy management of lifestyle, diet and nutritional supplements can mitigate the disease progression in population. Simultaneously early screening of PCOS in adolescence provides various interventions that eventually moderate the chronic metabolic sequelae of 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 highlighted the significant involvement of the trace metals towards negative health consequences. Hence schemes and strong endorsements should be embattled to diminish human exposure to defend near future from this progressively intensifying adverse health effects.

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