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Review Article

Globalization, Obesity and Polycystic Ovary Syndrome: What We Pay?

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder of unknown etiology. During last decade several studies have been conducted to identify the underlying causes of PCOS that includes multi-genetic and environmental factors. In laboratory animals, exposure to environmental toxicants has been shown to disrupt ovarian and reproductive function in females, often at doses similar to typical levels of human exposure. In humans, heat shock proteins (HSPs) and endocrine disruptor chemicals (EDCs) especially, bisphenol A (BPA) are increased due to globalization that play a role in the women with PCOS, which further complex by life styles. Still efforts are going on to dissect out the pathophysiology of the syndrome, and future research is required to unravel the mechanisms by which BPA, heat stress, obesity, adiponectin, insulin resistance (IR) etc., may contribute to PCOS and the critical periods of exposure too, which may even have transgenerational consequences. This review briefly discuss the current knowledge of the pathogenesis of PCOS along with the impact of climate change scenario and life style factors; and also throw a light on the future direction of research. For this purpose, data were mainly identified and presented through Pubmed, Medline, Toxline, Research Gate and web browser (Google) searching using numerous combinations of terms pertaining to different aspects of PCOS.

Keywords: Climate change; Globalization; PCOS; EDCs; BPA, HSPs; Obesity; IR; Life style

Author Contribution

NN conceived and designed the review, and draw the illustration. **NN, RD, JRDF** and **AB** performed literature survey and wrote the review. The authors sequence is based on the quantum of work done in the period. All authors have read and approved the manuscript.

Abbreviations

PCOS: Polycystic Ovary Syndrome; HSPs: Heat Shock Proteins; EDCs: Endocrine Disruptor Chemicals; BPA: Bisphenol A; BPS: Bisphenol S; IR: Insulin Resistance; T2DM: Type II Diabetes; SHBG: Sex Hormone Binding Globulin; IGF: Insulin Growth Factor; IGFBP: Insulin Like Growth Factor Binding Protein; BMI: Body Mass Index; CV: Cardiovascular; Zn: Zinc; Cu: Copper; Mn: Manganese; Mg: Magnesium; Cd: Cadmium; Co: Cobalt; Pb: Lead; ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase; Vaspin: **V**isceral **A**dipose tissue-derived **S**erine **P**rotease **In**hibitor; HRQOL: **H**ealth **R**elated **Q**uality **o**f **L**ife

Introduction

Climate change is the planet's biggest threat in the 21st century, affecting several health issues in young men and women through its potential effects on extreme weather, heat stress, food and water consumption, obesity and life style. Among the climatic variables, temperature and humidity are common environmental stressors that have great impact on the fertility of mammals across the globe by altering hormonal and physiological profiles, signaling cascades and compromising developmental competence of the embryo. Also in recent decade, the range of potentially relevant environmental factors broadens to include environmental chemicals, which could constantly change the climate of our surrounding due to rapid industrialization and globalization. Therefore, the exposure of potential hazardous substances are now given great consideration in reviewing and assessing the increasing risk of reproductive disorders such as, menstrual irregularities, early menarche, uterine and breast fibrosis, polycystic ovary syndrome (PCOS) and subfertility in the young women that too add economical and psychological pressure on the society. PCOS is a multi-factorial disorder with various genetic, endocrine and environmental abnormalities, which is a common cause of infertility and pregnancy complication.

PCOS Prevalence, Signs and Symptoms

PCOS, the most common and complex endocrine disorders in the women worldwide [1] that affecting 5-20% of the reproductive age group women [2,3] with 9–36% prevalence in the adolescent girl only [4]. These wide variations in prevalence may be due to heterogeneous presentation of the symptoms, diagnostic criteria practiced, limitations in diagnosis, age groups, and ethnicity. With the cause of PCOS being idiopathic and currently unknown, various researches have shown that environmental factors such as, endocrine disrupting chemicals (EDCs) especially, bisphenol A (BPA), poor nutrition and diet, obesity, insulin resistance (IR), type II diabetes (T2DM) and hormonal imbalances contribute to hyperandrogenism, ovulary dysfunction (chronic anovulation) and polycystic ovaries, the major symptoms of PCOS [5]. According to a study, 44% of the women with PCOS are obese [6]. A secondary

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study linking PCOS and obesity goes on to confirm that weight loss of 5% show significant improvements in the symptoms, and therefore, it can be said that obesity has a strong link to the development of PCOS [7]. Hyperandrogenism, perhaps the most consistent and obvious diagnostic feature of PCOS, is assessed clinically by acne, hirsutism and alopecia, and also by biochemical indices, including free testosterone and sex hormone binding globulin (SHBG), and increasing LH : FSH ratio [8,9]. De Leo et al., demonstrated low aromatase activity in the PCOS patients, which is a granulosa cell enzyme that converts androgens into estrogens, which may be partly responsible for hyperandrogenism in this syndrome. Elevated levels of androgens have a negative impact on follicular development, causing atresia, as well as ovarian development, inhibiting meiotic maturation by decreasing oscillations of intracytoplasmic calcium levels [10]. Further, a significant increase in the insulin growth factor (IGF)-1/insulin like growth factor binding protein (IGFBP)-1 in the theca cells induces androgen production in PCOS. Moreover, IGF-1 and IGFBP-1 stimulate estrogen production by the granulosa cells, and synergically act with FSH and LH in modulating the expression of aromatase; and also exert an indirect control on ovarian steroidogenesis like, insulin through hypothalamus-pituitary-ovarian axis [10,11]. Moreover, Hughes et al., revealed that genes involve in steroidogenesis such as, genes of retinoic acid biosynthesis and LH-stimulated gene pathways, are generally up-regulated in PCOS, whereas genes involve in Wnt signaling pathway appear to be down-regulated [12]. Immune response genes and those involve in apoptosis are also altered in PCOS, but the net effect of these alterations is unclear; though there is a possibility of diagnostic biomarker for PCOS. Partly due to PCOS definition, 60–80% of the women with PCOS have abnormally elevated circulating testosterone [13]. These clinical characteristics and biochemical indices can vary greatly among the individuals depending on many factors as mentioned-above as well as body mass index (BMI).

The signs and symptoms of PCOS often appear in childhood and adolescent, indicating fetal and early postnatal molecular events are responsible. Though guidelines are not available for PCOS management in children, but in young girls diagnosis is based on the exclusion of other causes of excess androgen and inappropriate menstrual cycle. The diagnosis of PCOS faces several challenges such as, difficulty of menstrual irregularity-based diagnosis, BMI and androgen variations in adolescence, common pre-pubertal hirsutism and acne, IR in pubertal children, adolescence, and regular menstrual cycle with polycystic ovaries [14]. However, thyroid function test, fasting glucose test, lipid level test, vaginal ultrasound and pelvic examination by doctors along with medical history etc. are the common management system of PCOS till date.

EDCs and PCOS Development

A major environmental factor link to PCOS is EDCs. Since World War II, advancement in worldwide production and use of chemicals increase exponentially. Over 80,000 chemicals are now used in US alone and approximately 1500 new chemicals are introduced every year [15]. Of these, at least 870 are documented EDCs, and because most of the chemicals in production have not been tested for adverse health effects, it is almost certain that more EDCs are yet to be identified [16], but what is not realized is that EDCs like, pesticides are persistent in living organisms and can accumulate in fat over the years [1]. EDCs can mimic endogenous hormones and/or interfere with the production, secretion, transportation, metabolism, binding action and excretion of the natural hormones. Originally, EDCs are thought to act by interfering with hormone binding at classical nuclear receptors; but today, it is well established that EDCs have numerous modes of actions and can also interfere with transcriptional factors, non-steroid receptors (i.e., neurotransmitter receptors), orphan receptors (aryl hydrocarbon receptor) and enzymatic activity [17,18], leading to altering reproductive function, neurodevelopment and metabolism, increasing cancer risk, and many more. Hence, understanding the mechanism of action of EDCs is the first step towards the problem associate with PCOS. According to Minf et al., EDCs have an affinity for androgen receptors; however, they can bind to many other hormonal receptors too [19]. Once bound, EDCs can either become active and mimic the action of the receptor with which it bound, or stay inactive and block the receptor sites making it unavailable, thus inhibit the receptors action.

Some EDCs, such as BPA and certain phthalates, are found in the environment that have significant body burden [20]. Further, alteration of serum phthalates, polychlorinated biphenyls, perfluorinated compounds, BPA etc. in the PCOS patients are in consistent with the anti- androgenic effects of phthalates as observed by Vagi et al., [21]. In animal models with no direct exposure to EDCs even as the germ cells, can show increase incidence of PCOS-like symptoms following exposure of EDCs to the generations earlier [22-25]. Importantly, exposure at low doses may be linked to adverse health effects because of non-monotonic dose-response relationship of EDCs [26]. Complicating the issue, a typical person has measureable levels of dozens of EDCs at once, and very little is known about the health risks associated with the chemical mixtures [27]. However, it is plausible that EDCs may contribute to the etiology of PCOS along with other factors, or may modify the presentation of this highly heterogeneous disorder. Thus far, the preponderance of research has focused on a single EDC, BPA, and for that reason it is the focus of the current review also.

Direct and Indirect Effects of BPA in PCOS

BPA ($C_{15}H_{16}O_2$), a synthetic compound, a xenoestrogen, is one of the most abundant EDCs in the environment that leaches out during the production of polycarbonate plastics and epoxy resins; hence, found in daily use plasticwares, water bottles, overhead water storage tanks, packaging for food and drink, and dental materials [28]. A positive correlation is observed between plastic usage and the reproductive disorders in the young women [29,30]. BPA and another analogue, Bisphenol S (BPS, $C_{12}H_{10}O_4S$) are responsible for different types of female reproductive abnormalities including interference of hypothalamic-pituitary hormonal axes, ovarian folliculogenesis, oocytes development and receptivity, resulting in reproductive disorders, disruption of androgen metabolism in the liver and lastly, infertility [31]. Apart from its well-known estrogen-mimetic properties, BPA plays a role in androgen metabolism. There are several lines of evidences indicating the existence of a bi-directional interaction between BPA and androgens. Specifically, it has been reported that uridine diphosphate-glucuronosyl transferase activity, a liver enzyme involve in BPA clearance from circulation,

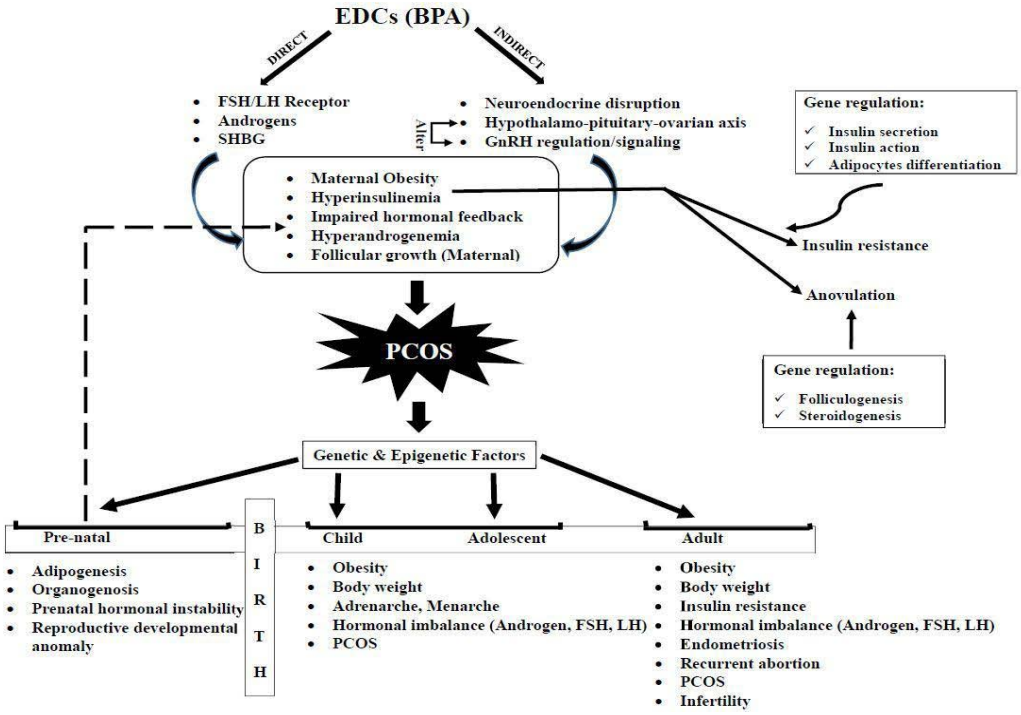

Figure 1: Critical period of EDCs (BPA) affecting PCOS in life time, contributing reproductive and metabolic interference through genetic and epigenetic predisposition (Naha N, 2017).

is down-regulated by androgens [32]. Additionally, BPA is a potent SHBG ligand and, accordingly, in high concentrations, displaces androgens from SHBG binding sites, leading to increase circulating free androgen concentrations [33]. Moreover, BPA significantly inhibits the activity of two different testosterone hydroxylases i.e., 2- and 6-hydroxylase, resulting in decreases testosterone catabolism and indirectly increases testosterone concentrations [34].

Androgens actually interfere with the removal of BPA from body, and disruption of androgen metabolism along with this phenomenon work in synergy to create hyperandrogenemia [28,35]. In fact, as compared to estrogenic compound diethylstilbestrol and genistein, BPA directly exerts its effect on SHBG, androgens, and FSH and LH receptors, leading to endometriosis, endometrial hyperplasia, recurrent abortion and PCOS. The significant positive association with PCOS is supported by increasing serum androgen level and BPA concentration in the neonatal rats, manifested by hyperanrogenemia, anovulation, ovarian cysts, high GnRH and dysregulation of insulin secretion and glucose metabolism [36]. *In utero* exposure in mice causes transgenerational effects as evidenced by fewer pregnancies in the progeny [37,38]. Further, BPA indirectly affects ovarian function by re-programming the neuroendocrine axis. The cell- or tissue-specific activity of BPA depends on the differential expression of the estrogen receptor variants and signaling cascades activated by them due to affinity of the aryl hydrocarbon receptor, estrogen receptor subfamily ER-α and ER-β, membrane bound estrogen receptor GPR30 and orphan nuclear receptor subfamily of estrogen related receptor ERR-α, ERR-β and ERR-γ with BPA and BPS [39,40]. The initial rise of BPA in the first half of pregnancy followed by significant reduction in the late stage reveals transportation of BPA to the amniotic fluid and accumulates in the uterine cavity during first half due to its low metabolic clearance [28].

Another very interesting point connecting BPA with PCOS is the observation that BPA *per se* may stimulates hyperandrogenemia in ovary, because *in vitro* culture of the rat ovarian theca-interstitial cells with BPA resulting in elevation of testosterone synthesis [41]. The mechanisms appear to be linked with the increase mRNA expression of the key enzymes of steroidogenesis, including 17-β hydroxylase, cholesterol side chain cleavage enzyme, and steroidogenic acute regulatory protein [41]. In PCOS, ovarian hyperandrogenism is partly attributed to the activation of this steroidogenic pathway [42]. Increase BPA levels in PCOS interacts with the ovary carrying an inherent enzymatic defect also, which leads to further enhancement of ovarian androgen production, and therefore, hyperandrogenemia as well as the anovulatory women [35]. Also high androgen level of uridine diphosphate-glucuronosyl transferase activity in the liver is reduced, which plays a role in metabolism and excretion of BPA [32]. This may partly explain why BPA concentrations are typically higher in males than in females in both the humans and the animals [43,44], and in the women with PCOS than the BMI-matched controls [28,35]. Tarantino et al., showed the women with BPA exposure suffering from PCOS and metabolic dysfunction such as, high IR, hepatic steatosis, spleen size and inflammation as compared to the control after adjusting BMI [45]. Prenatal BPA exposure is associated with lower BMI in the pre-pubertal girls; however, high level of BPA is linked with increase waist circumference and BMI [46]. High BPA in the adults is also related with diabetes, cardiovascular (CV) disease and abnormal liver enzyme levels [47]. Though circulating BPA concentrations correlate with BMI, but both the lean and obese women with PCOS showed BPA levels similar to the obese controls, but higher than the lean controls [35]. Therefore, in the women

with PCOS, BPA Levels appear to be comparable in the lean and the overweight groups.

Further, the time of exposure of BPA contribute to PCOS raise a serious concern, as for many EDCs, the period of exposure and clinical onset of disease coincide, sometimes in decades. For many chemicals, the greatest risk is the pre- and early post-natal period, when organ systems and endocrine homeostasis are established. For that reason, animal research on BPA and PCOS has targeted perinatal chemical exposure and transgenerational effects. The high doses of BPA is found during postnatal days1–10 of the rats upon subcutaneous exposure, which develops PCOS-like symptoms in the adulthood including increase serum testosterone and estradiol, reduce progesterone and ovarian cysts [36]. However, the analogous human studies targeting early exposure are logistically difficult though the examination of BPA exposure during adulthood is in reality. Overall, the prenatal and the early postnatal environment may play a role in this disorder; excessive androgens *in utero* cause PCOS supported by the animal experiments. Elevated androgen levels or activity in the fetus could promote PCOS-like symptoms later in life, at least under certain postnatal conditions. Further, intrauterine growth restriction by BPA may alters adipose tissue function, contributing to IR and possibly PCOS in later [28,48], which strengthen the fact that perinatal environment is crucial for the adult risk of PCOS, reproductive and metabolic interference through hypothalamic-pituitary- ovarian axis (Figure 1).

Moreover, EDCs, especially, BPA are strongly associated with the existence of PCOS that may imply an involvement of these chemical in PCOS pathophysiological mechanisms. Certainly, due to study design, the data do not detect causality in the pathophysiological mechanism linking BPA with PCOS. However, experimental data of the neonatal exposure to BPA and the subsequent development of PCOS in the animals are suggestive of a possible interaction of this abundant chemical with the hormonal and metabolic abnormalities as observed in the women with PCOS. BPA also affects adipocyte differentiation [49], inhibits adiponectin, protects against metabolic syndrome, and increases genes expression in adipocyte differentiation [50,51]. BPA activates glucocorticoid receptors; resulting in up-regulation of 11-β-hydroxysteroid dehydrogenase that catalyzes the conversion of cortisone to cortisol, thus further promoting adipogenesis [52]. It induces pancreatic β-cells to increase insulin production and disrupts glucose homeostasis, lower metabolism, thus suggesting one route by which BPA may promotes chronic hyperinsulinemia and IR [53-57]. In fact, current evidence suggests that pancreatic β-cell dysfunction by BPA exposure is mediated by mitochondrial activity and metabolic pathways [58]. BPA alters global DNA methylation in the murine preadipocyte fibroblasts too [59]. BPA also exacerbates normal pregnancy-related IR, resulting in reduced glucose tolerance and increased insulin, triglygeride, glycerol and leptin levels, and body weight compared to the controls even several months post-partum [60]. Kandakari et al., showed the degree of IR is statistically different between the PCOS and the control groups, and the lean and the obese subgroups with a positive correlation of BPA among the PCOS women; hence, speculated a possible impact of BPA in insulin action [28]. Animal study also showed the environmentally relevant doses of BPA are linked to disturbance of pancreatic physiology and glucose metabolism, thus enhancing the risk for IR development in the intact animals [56]. All together, these observations suggest many mechanisms by which BPA as one of the main EDCs may alter androgen and metabolic activity, and induce epigenetic modifications during PCOS or PCOS-like symptoms.

Role of Heat Shock Proteins, Trace Elements and Heavy Metals in PCOS

Heat shock proteins (HSP) are a family of chaperon proteins that are expressed at low levels under normal condition but are increased dramatically in response to exposure of cells to stressful conditions to modulate cellular function and protein homeostasis [61]. Ling et al., revealed knock-down of HSP10 induces apoptosis in mouse ovarian granulosa cells, whereas over expression suppresses apoptosis, suggesting HSP10 may regulates apoptosis in mouse ovary, and therefore possibly play a key role in development of PCOS [62]. Several studies indicated high serum HSP70 represents ovarian damage [63], disease severity in transgenic mice against oxidative/ischemic stress [64], and several chronic disorders including CV diseases and T2DM [65,66]. HSP70 also increases during heat stress [67]. Gao et al., identified HSP70 as an independent biomarker for PCOS as its serum level is elevated in the non-obese PCOS patients accompanying with notable positive correlations with IR index, HOMA-IR, oxidative stress and inflammatory markers link to CV risk and T2DM when compared to the age and BMI-matched healthy controls [68]. Release of ROS during oxidative stress triggers circulating markers in the women with PCOS, leading to oxidation and aggregation of vital proteins and DNA, ultimately resulting in failure of normal cell function [61]. Therefore, possibly HSP70 in the PCOS patients confers protection against lipid peroxidation and oxidative stress, and may be useful for global assessment of PCOS risk. Moreover, an isoform of HSP90, HSP90B1 that has a role in proliferation and survival of the ovarian cells, become up-regulated and promotes the granulose cell proliferation in the pathogenesis of PCOS [69]. But HSP90B1 knock-down increases caspase-3 activity and apoptosis in the ovarian cells [69], suggesting modulation of HSP90B1 activity via molecular intervention become useful strategy for PCOS management.

Essential trace elements have four major functions as being stabilizers, elements of structure, essential elements for hormonal function and cofactors in enzymes. Trace elements such as, zinc (Zn), copper (Cu), manganese (Mn), magnesium (Mg) are involved in cell metabolism and regulatory pathways that controlling oxidative stress, whereas heavy metals such as, cadmium (Cd), cobalt (Co), lead (Pb) etc. play a role in the formation of reactive oxygen species (ROS) and increasing membrane lipid peroxidation; thereby promoting oxidative stress. Excessive ROS and hence, oxidative stress is associated with PCOS in the patients [70], suggesting a relation between trace elements, heavy metals and PCOS, link to the redox homeostasis. Studies also found that Cu induces oxidative stress by catalyzing ROS formation and glutathione depletion in the PCOS patients [71]. Kuscu and Var showed high Superoxide Dismutase (SOD) in the PCOS patients [72]. But according to Kurdoglu et al., serum Zn level is higher in the patients with PCOS, but serum Mn is half of the corresponding serum levels of the controls [73]. Since oxidative stress is increased in PCOS; therefore, it is possible that serum Mn level is decreased due to consumption in the antioxidant defense system including Mn-SOD. But no statistical significance is

observed in between serum Mg and age, BMI and testosterone in this study. In contrast, low serum Mg in the PCOS patients is reported by Muneyyirci-Delale et al., [74] though Kauffman et al., noted no significant difference between the PCOS patients and the controls with respect to serum Mg level [75]. Further, heavy metals Pb and Co induce free radical-mediated DNA damage, whereas Cd though not contributing free radicals directly, but indirectly forms ROS. Kurdoglu et al., found low serum Pb level and inverse correlation with total testosterone in the PCOS patients, but serum Co and Cd levels remain within the normal range [73].

Obesity, IR, T2DM and Metabolic Aspects of PCOS

PCOS is not just limited to these above conditions; it can also be accompanied by obesity and metabolic aspects discussed below, which confirm that all these factors play a pivotal role in the pathogenesis of PCOS; and need to be included as a factor during diagnosis of the syndrome. Gupta et al., summarized the common metabolic signaling pathways in a heterogeneous population of the PCOS patients, indicating that the altered protein/gene expression profiles are relevant to glucose and lipoprotein metabolism, cell proliferation, apoptosis and IR [76]. High IR is the central feature of PCOS as a prevalence of 25–60% the women with PCOS is accompanied by IR, oxidative stress and chronic low-grade inflammation [77]. Using euglycemic hyperinsulinemic clamp technique, Holte et al., showed a significant correlation between abdominal fat mass and IR [78]. Several studies also demonstrated that the obese PCOS women have lower insulin sensitivity and T2DM than the age- and body weight-matched controls, which further leads to severe IR state [79,80]. In US, 70% of the women with PCOS are IR, and prospective clinical studies among them have revealed a 7.5–10% prevalence of T2DM compared to 0.7% prevalence in the healthy young women [9]. Furthermore, the conversion rate from impaired glucose tolerance to frank diabetes is 5–10 folds higher in the women with PCOS compared with the non-PCOS women in both US and Australia [9]. Also more than half of the normal weight PCOS and majority of the obese PCOS women are IR, and a significant number develop T2DM by the age of 40 yr [81,82]. Ehrmann et al., also suggested a 5–10 folds increase in conversion from impaired glucose tolerance to T2DM [83]. Presence of PCOS is higher in the women with T2DM than in the non-diabetic women as shown by Peppard et al. [84].

Upon hyperglycemia, stimulation of ROS generation from the mononuclear cells may serves as an inflammatory trigger for the induction of IR in PCOS [70]. Thus PCOS and its metabolic complications may be explained by the existence of the potential interaction among these factors, and the clinical heterogeneity may be explained by the individual variability in the relative contributions of this interaction. De Leo et al., reported the higher risk of metabolic and CV diseases, and the related morbidity in the PCOS patients as compared to the general population [10]. Block et al., reported the role of obesity in inflammatory processes relevant to CV risk in the women with PCOS [85]. Both the lean and the obese PCOS women have peripheral IR and hyperinsulinemia. In Indian population, studies showed relation of PCOS with hypertension, diabetes and endometrial hyperplasias mainly in the obese, and increasing the risk of morbidity at a much younger age than the lean ones [86]. Moreover, oxidative stress in PCOS is associated with hyperglycemia and hyperinsulinemia [70]. ROS release during oxidative stress triggers circulating markers in the women with PCOS, leading to oxidation and aggregation of vital proteins and DNA, resulting in the failure of normal cell function. Nakhjavani et al., showed association of IR with obesity or habitual consumption of fatty diets link to increase cellular levels of stored triglycerides and fatty acid derivatives, increase expression of HSP70 etc., manifested by pathogenesis of IR disorders such as, metabolic syndrome and T2DM [65]. This involvement appears to be bi-directional, because not only does HSP70 accumulation favors IR and contributes to pancreatic β-cell dysfunction and diabetes, but also facilitates HSP70 accumulation within the body during PCOS.

Adipokines, the secretory proteins of adipose tissue have multiple functions including modulation of inflammation and obesity, leading to other metabolic disorders [87,88]. With regards to inflammation, pro- and anti-inflammatory adipokines are crucial in determining the homeostasis related to nutrition, as elevation of pro-inflammatory adipokines and lowering of anti-inflammatory adipokines is found in the rodents and the humans linked with obesity. Mostly adipokines are pro-inflammatory with a few exceptions of adiponectin, such as, a secreted frizzled-related protein 5, visceral adipose tissue-derived serine protease inhibitor (Vaspin) and omentin-1. Many revent studies have also shown an alteration of adipokine secretion in the PCOS women [89,90]. Further, the women with PCOS manifest distribution of visceral fat in the abdominal region as opposed to the thighs and hips. Abdominal distribution of fat is associated with high risk of IR, diabetes and lipid abnormalities [91]. Studies also shown that the obese PCOS women have significantly lower SHBG plasma levels compared to their non-obese counterparts, which further worsen hyperandrogenism along with menstrual disturbances and hirsutism [92]. The PCOS women further have higher lipid profile, lower level of high-density lipoprotein cholesterol and higher concentration of very low-density lipoprotein [93]. The patients with PCOS show higher levels of leptin and other pro- inflammatory adipokines such as, visfatin and vaspin etc., while lower levels of adiponectin and omentin in the young population. A study showed that the PCOS women had lower levels of adiponectin with IR as compared to the non PCOS control group with a similar BMI, suggesting serum adiponectin levels are not governed entirely by the degree of adiposity in the women [94]. Moreover, the family history of PCOS and IR can be correlated with significantly lower adiponectin levels in the PCOS women below 25 years of age that may worsen over time [95]. Modest weight loss of 5–10% of initial body weight has been demonstrated to improve many of the features of PCOS [96]. Hence, therapy should focus on both the short- and long-term reproductive, metabolic and psychological features. Given the aetiological role of IR and the impact of obesity on both hyperinsulinemia and hyperandrogenism, multidisciplinary life style improvement aimed at normalizing IR, improving androgen status and aiding weight management are recognized as a crucial initial treatment strategy [96].

Life Style Factors and PCOS Management

Fast food and competitive food such as, cheese, burgers, French fried potatoes, sugar sweetened beverages etc. are typically called 'junk food', rich in refined starch, added sugars, saturated fats and

total carbohydrates with less dietary fibers. These foods are popular among the adolescents and youths, which compromise the diet quality, imbalance in the energy intake and increase the risk of obesity [97], thereby affecting body weight, and displacing better and healthy food options that raises serious public health concerns, especially, in the children and the adolescents. In US, studies has been found that person who eat more junk food consume more calorie per day on an average as compared to the ones who do not [98,99]. Jeffery et al., reported an association between people frequently eating from the fast food restaurants with higher body weight and unhealthy eating habits [100]. The women suffering from PCOS present an increase quantity of visceral fat in the obese, overweight and also in the normal weight patients [101]. At the present global situation, increasing rates of obesity and unhealthy dietary habits, canned drink along with sedentary life style are the causative factors of generating PCOS and/or PCOS-like symptoms among the adolescent and young girls [102]. Therefore, life style changes remain a concern for the young women with PCOS. Thus, PCOS management should focus on support, awareness, knowledge and education among the adolescent, young and adult women of reproductive age, and needs to strongly emphasize the healthy life style with targeted medical therapy as required [96].

Life style modifications is important as the first-line treatment because life style changes such as, diet, exercise and behavioral modifications appear to improve the metabolic and reproductive abnormalities of the overweight and the obese patients with PCOS [103]. But life style modification affects a woman physically as well as mentally, so psychological, behavioral and emotional supports are valuable while treating such cases. Farell and Antoni indicated as improve physiological processes with the result of improving IR, hypothalamo-pituitary-adrenal axis functioning, obesity and hyperandrogenism, PCOS may be alleviated and incidence of PCOS among the adolescents can be reduced, suggesting medical management of PCOS would benefit greatly from inclusion of psychological and/or behavioral and emotional approaches [9]. Further, Elmenim and Emam revealed life style modifications create positive psychological effects including mood and psychological well- being, stress management, decrease depression and anxiety, and increase self-esteem and health related quality of life (HRQOL) scores for the women with PCOS [104]. Hence, the first line therapy for PCOS involves life style modifications, including alcohol, caffeine, smoking, psychological stressors, nutritional counseling and exercise etc., to help stave off the threat of diabetes, childhood and/or adolescent obesity by promoting sustainable weight loss and improving glucose metabolism that contribute to stabilize this distressing syndrome among the affected population [105]. However, when efforts at life style therapy are inadequate or unsuccessful, medications are selected based on the patient-specific metabolic disorders including IR, anovulation and menstrual irregularities link to high androgen level [106].

Conclusion and Future Direction of Research

The most interesting and unexpected findings of the recent research on this issue in present scenario is the women with PCOS, BPA levels are higher compared with the BMI-matched healthy women, and are positively associated with the hormonal and metabolic abnormalities characterizing the syndrome. Further, transgenerational effects of BPA and other EDCs like, phthalates, vinclozolin, dioxin, pesticides, jet fuel etc. in the animals are extended not only in the generation with gestational exposure (F1) or their offspring (F2), but also in the subsequent generation (F3) who never exposed at all directly, resulting in declined fertility, disrupted pubertal development, primordial follicle loss, polycystic ovaries and so on, that relevant to human PCOS symptoms, suggesting a potential role of several EDCs in PCOS pathophysiology. To our knowledge, prenatal or early postnatal exposure of EDCs in the humans has not conducted to assess PCOS incidence in the female infants, children, and girls approach to adolescence and adulthood. Also limited studies are reported on trace elements, heavy metals and other EDCs except BPA in PCOS, as well as small subject size in the available human studies. Moreover, the humans unlike the animals expose to dozens of chemicals at a time, so combinations of exposures may contribute to this disorder. This is obviously a challenge for research on human population due to long intergenerational interval and virtually continuous exposure to chemicals in the modern environment.

Thus, we propose four promising future direction of research. First, pre-clinical and clinical investigations targeting increase risk generations after the initial exposure and subsequent epigenetic signature to elucidate the possible mechanism of PCOS pathogenesis link to broad-spectrum EDCs and other new chemicals with potential disrupting capacity of estrogen, androgen and metabolic pathways, and causing PCOS and/or PCOS-like symptoms. Second, further research into "mixtures" of chemicals including low doses though complicated but more relevant on reproductive disease/disorder in the current climate change scenario. Third, based on pre-clinical data that contribute to prenatal programming of endocrine and reproductive function by BPA, development of PCOS in a longitudinal cohort upon early life exposure in order to provide new insights of PCOS. Finally, signaling pathways considering several up- and down-stream molecules especially, different HSPs and their isoforms, adipokines especially, adiponectin and its receptors etc. in further translational research to improve our understanding of the molecular mechanism of PCOS development, diagnosis and therapeutic alternative for the women suffering from PCOS.

Conflict of Interest

None.

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References

1. Diamanti-Kandarakis E, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. Endocrine. 2006; 30: 19-26.

2. Diamanti-Kandarakis E. Polycystic ovarian syndrome: Pathophysiology, molecular aspects and clinical implications. Expt Rev Mol Med. 2008; 10.

3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004; 81: 19-25.

4. Nair MK, Pappachan P, Balakrishnan S, Leena ML, George B, Russell PS. Menstrual irregularity and poly cystic ovarian syndrome among adolescent girls: A 2 year follow-up study. Ind J Pediatr. 2012; 79: 69-73.

5. Le TN, Wickham Iii EP, Nestler JE. Insulin sensitizers in adolescents with polycystic ovary syndrome. Min Pediatr. 2017.

6. Carmina E, Lobo RA. Polycystic Ovary Syndrome (PCOS): Arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab. 1999; 84: 1897-1899.

7. Barber TM, Mc Carthy MI, Wass JAH, Franks S. Obesity and polycystic ovary syndrome. Clin Endocrinol. 2006; 65: 137-145.

8. Azziz R. PCOS: A diagnostic challenge. Reprod Biomed Online. 2004; 8: 644-648.

9. Farrell K, Antoni M. Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: Biobehavioral mechanisms and interventions. Fertil Steril. 2010; 94: 1565-1574.

10. De Leo V, Musacchio MC, Cappelli V. Genetic, hormonal and metabolic aspects of PCOS: An update. Reprod Biol Endocrinol. 2016; 14: 38-54.

11. Mukherjee S, Maitra A. Molecular and genetic factors contributing to insulin resistance in polycystic ovary syndrome. Ind J Med Res. 2010; 131: 743-460.

12. Hughes C, Elgasim M, Layfield R, Atiomo W. Genomic and post-genomic approaches to polycystic ovary syndrome - progress so far: Mini review. Hum Reprod. 2006; 21: 2766-2775.

13. Chang WY, Knochenbauer ES, Bartolucci AA, Azziz R. Phenotypic spectrum of polycystic ovary syndrome: Clinical and biochemical characterization of the three major clinical subgroups. Fertil Steril. 2005; 83: 1717-1723.

14. Bremer AA. Polycystic ovary syndrome in the pediatric population. Metab Syndr Relat Disord. 2010; 8: 375-394.

15. Woodruff TJ. Bridging epidemiology and model organisms to increase understanding of endocrine disrupting chemicals and human health effects. J Steroid Biochem Mol Biol. 2011; 127: 108-117.

16. WHO. State of the science of endocrine disrupting chemicals. Bergman A, Heindel JJ, Jobling S et al (Ed.). Geneva, Switzerland. 2012.

17. Welshons WV, Nagel SC, vom Saal FS. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology. 2006; 147: 56- 69.

18. Matsushima A, Kakuta Y, Teramoto T, et al. Structural evidence for endocrine disruptor bisphenol A binding to human nuclear receptor ERR gamma. J Biol Chem. 2007; 142: 517-524.

19. Mnif W, Hassine AIH, Bouaziz A, Bartegi A, Thomas O, Roig B. Effect of Endocrine Disruptor Pesticides: A Review. Int J Env Res Pub Health. 2011; 8: 2265-2303.

20. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Env Health Persp. 2011; 119: 878-885.

21. Vagi S, Baumgartner EA, Sjodin A, et al. Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol A in polycystic ovary syndrome: A case–control study. BMC Endocr Disor. 2014; 14: 86-97.

22. Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. Endocrinology. 2006; 147: 43-49.

23. Manikkam M, Tracey R, Guerrero-Bosagna C, et al. Dioxin induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. PLoS ONE. 2012; 7: 46249.

24. Manikkam M, Tracey R, Guerrero-Bosagna C, et al. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS ONE. 2013; 8: 55387.

25. Tracey R, Manikkam M, Guerrero-Bosagna C, et al. Hydrocarbons (jet fuel JP-8) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. Reprod Toxicol. 2013; 36: 104-116.

26. Vandenberg LN, Colborn T, Hayes TB et al. Hormones and endocrine-disrupting chemicals: Low dose effects and non-monotonic dose responses. Endocr Rev. 2012; 33: 378-455.

27. Kortenkamp A. Low dose mixture effects of endocrine disrupters: Implications for risk assessment and epidemiology. Int J Androl. 2008; 31: 233-240.

28. Kandaraki E, Chatzigeorgiou A, Livadas S, Palioura E, Economou F, Koutsilieris M, et al. Endocrine disruptors and polycystic ovary syndrome: Elevated serum levels of bisphenol A in women with PCOS. Clin Endocrinol Metab. 2011; 96: 480-484.

29. Meeker JD, Sathyanarayana S, Swan SH. Phthalates and other additives in plastics: Human exposure and associated health outcomes. Philos Trans R Soc Lond B Biol Sci. 2009; 364: 2097-2113.

30. Caserta D, Mantovani A, Marci R, Fazi A, Ciardo F, La Rocca C, et al. Environment and women's reproductive health. Hum Reprod Update. 2011; 17: 418-433.

31. Markey CM, Coombs MA, Sonnenschein C, et al. Mammalian development in a changing environment: Exposure to endocrine disruptors reveals the developmental plasticity of steroid hormone target organs. Evol Dev. 2003; 5: 67-75.

32. Takeuchi T, Tsutsumi O, Ikezuki Y, Kamei Y, Osuga Y, Fujiwara T, et al. Elevated serum bisphenol A levels under hyperandrogenic conditions may be caused by decreased UDP-glucuronosyltransferase activity. Endocr J. 2006; 53: 485-491.

33. De chaud H, Ravard C, Claustrat F, de la Perrie re AB, Pugeat M. Xenoestrogen interaction with Human Sex Hormone-Binding Globulin (hSHBG). Steroids. 1999; 64: 328-334.

34. Hanioka N, Jinno H, Nishimura T, Ando M. Suppression of male-specific cytochrome P450 isoforms by bisphenol A in rat liver. Arch Toxicol. 1998; 72: 387-394.

35. Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocr J. 2004; 51: 165-169.

36. Fernandez M, Bourguignon N, Lux-Lantos V. Neonatal exposure to bisphenol a and reproductive and endocrine alterations resembling the polycystic ovarian syndrome in adult rats. Env Health Persp. 2010; 118: 1217-1222.

37. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics and disease. Reprod Toxicol. 2011; 31: 363-373.

38. Mileva G, Baker SL, Konkle ATM, Bielajew C. Bisphenol A: Epigenetic reprogramming and effects on reproduction and behavior. Int J Env Res Pub Health. 2014; 11: 7537-7561.

39. Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al. *In vitro* molecular mechanisms of bisphenol A action. Reprod Toxicol. 2007; 24: 178-198.

40. Takayanagi S, Tokunaga T, Liu X, et al. Endocrine disruptor bisphenol A strongly binds to human estrogen receptor γ (ERRγ) with high constitutive activity. Toxicol Lett. 2006; 167: 95-105.

41. Zhou W, Liu J, Liao L, Han S, Liu J. Effect of Bisphenol A on steroid hormone production in rat ovarian theca-interstitial and granulosa cells. Mol Cell Endocr. 2008; 283: 12-18.

42. Nelson VL, Qin Kn KN, Rosenfield RL, Wood JR, Penning TM, Legro RS, et al. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001; 86: 5925-5933.

43. Takeuchi T and Tsutsumi O. Serum bisphenol a concentrations showed gender differences, possibly linked to androgen levels. Biochem Biophys Res Commun. 2002; 291: 76-78.

44. Takeuchi T, Tsutsumi O, Nakamura N. Gender difference in serum bisphenol A levels may be caused by liver UDP-glucuronosyltransferase activity in rats. Biochem Biophys Res Commun. 2004; 325: 549-554.

45. Tarantino G, Valentino R, Di Somma C. Bisphenol A in polycystic ovary syndrome and its association with liver-spleen axis. Clin Endocrinol (Oxf).

2013; 78: 447-453.

46. Harley KG, Aguilar Schall R, Chevrier J. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. Env Health Persp. 2013; 121: 514-520.

47. Lang IA, Galloway TS, Scarlett A. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. J Am Med Assoc. 2008; 300: 1303-1310.

48. de Zegher F, Lopez-Bermejo A, Ibanez L. Adipose tissue expandability and the early origins of PCOS. Trends Endocrinol Metab. 2009; 20: 418-423.

49. Masuno H, Iwanami J, Kidani T, et al. Bisphenol A accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. Toxicol Sci. 2005; 84: 319-327.

50. Hugo ER, Brandebourg TD, Woo JG, et al. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. Env Health Persp. 2008; 116: 1642-1647.

51. Phrakonkham P, Viengchareun S, Belloir C. Dietary xenoestrogens differentially impair 3T3-L1 preadipocyte differentiation and persistently affect leptin synthesis. J Steroid Biochem Mol Biol. 2008; 110: 95-103.

52. Wang J, Sun B, Hou M. The environmental obesogen bisphenol A promotes adipogenesis by increasing the amount of 11-β-hydroxysteroid dehydrogenase type 1 in the adipose tissue of children. Int J Obesity. 2013; 37: 999-1005.

53. Nadal A, Alonso-Magdalena P, Soriano S. The pancreatic β-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. Mol Cell Endocrinol. 2009; 304: 63-68.

54. Alonso-Magdalena P, Ropero AB, Carrera MP, Cederroth CR, Baquie M, Gauthier BR, et al. Pancreatic insulin content regulation by the estrogen receptor ER α. PLoS ONE. 2008; 3: 2069.

55. Batista TM, Alonso-Magdalena P, Vieira E. Short-term treatment with bisphenol A leads to metabolic abnormalities in adult male mice. PLoS ONE. 2012; 7: 33814.

56. Alonso-Magdalena P, Morimoto S, Ripoll C, Fuentes E, Nadal A. The estrogenic effect of bisphenol A disrupts pancreatic β-cell function *in vivo* and induces insulin resistance. Env Health Persp. 2006; 114: 106-112.

57. Ropero A, Alonso-Magdalena P, Garcia-Garcia E. Bisphenol A disruption of the endocrine pancreas and blood glucose homeostasis. Int J Androl. 2008; 31: 194-200.

58. Nappi F, Barrea L, Di Somma C, et al. Endocrine aspects of environmental obesogen pollutants. Int J Env Res Public Health. 2016; 13: 765-780.

59. Bastos SL, Kamstra J, Cenijn P, et al. Effects of endocrine disrupting chemicals on *in vitro* global DNA methylation and adipocyte differentiation. Toxicol *in vitro*. 2013; 27: 1634-1643.

60. Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, et al. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Env Health Persp. 2010; 118: 1243-1250.

61. Kalmar B and Greensmith L. Induction of heat shock proteins for protection against oxidative stress. Adv Drug Deliv Rev. 2009; 61: 310-318.

62. Ling J, Zhao K, Cui YG, Li Y, Wang X, Li M, et al. Heat shock protein 10 regulated apoptosis of mouse ovarian granulosa cells. Gynecol Endocrinol. 2011; 27: 63-71.

63. Narayansingh RM, Senchyna M, Vijayan MM, Carlson JC. Expression of Prostaglandin G/H Synthase (PGHS) and Heat Shock Protein-70 (HSP-70) in the Corpus Luteum (CL) of prostaglandin F2 alpha-treated immature superovulated rats. Can J Physiol Pharmacol. 2004; 82: 363-371.

64. Marber MS, Mestril R, Chi SH et al. Over expression of the rat inducible 70-kD heat stress protein in a transgenic mouse increases the resistance of the heart to ischemic injury. J Clin Invest. 1995; 95: 1446- 1456.

65. Nakhjavani M, Morteza A, Khajeali L, et al. Increased serum HSP70 levels are associated with the duration of diabetes. Cell Stress Chaper. 2010; 15: 959-964.

66. Zhang X, Xu Z, Zhou L et al. Plasma levels of HSP70 and anti-HSP70 antibody predict risk of acute coronary syndrome. Cell Stress Chaper. 2010; 15: 675-686.

67. Vince RV, Oliver K, Midgley AW, McNaughton LR, Madden LA. *In vitro* heat shock of human monocytes results in a proportional increase of inducible HSP70 expression according to the basal content. Amino Acids. 2010; 38: 1423-1428.

68. Gao H, Meng J, Xu M, Zhang S, Ghose B, Liu J, et al. Serum heat shock protein 70 concentration in relation to polycystic ovary syndrome in a non-obese Chinese population. PLoS ONE. 2013; 8: 67727.

69. Li L, Mo H, Zhang J, et al. The role of heat shock protein 90B1 in patients with polycystic ovary syndrome. PLoS ONE. 2016; 11: 0152837.

70. Gonzalez F, Rote NS, Minium J, Kirwan JP. Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. J Clin Endocrinol Metab. 2006; 91: 336-340.

71. Dinger Y, Akcay T, Erdem T, Ilker Saygili E, Gundogdu S. DNA damage, DNA susceptibility to oxidation and glutathione level inwomen with polycystic ovary syndrome. Scand J Clin Lab Invest. 2005; 65: 721-728.

72. Kuscu NK and Var A. Oxidative stress but not endothelial dysfunction exists in non-obese, young group of patients with polycystic ovary syndrome. Acta Obstet Gynecol Scand. 2009; 88: 612-617.

73. Kurdoglu Z, Kurdoglu M, Demir H, Sahin HG. Serum trace elements and heavy metals in polycystic ovary syndrome. Hum Expt Toxicol. 2012; 31: 452-456.

74. Muneyyirci-Delale O, Nacharaju VL, Dalloul M. Divalent cations in women with PCOS: Implications for cardiovascular disease. Gynecol Endocrinol 2001; 15: 198-201.

75. Kauffman RP, Tullar PE, Nipp RD, Castracane VD. Serum magnesium concentrations and metabolic variables in polycystic ovary syndrome. Acta Obst Gynecol Scand. 2011; 90: 452-458.

76. Gupta S, Ghulmiyyah J, Sharma R, Halabi J, Agarwal A. Power of proteomics in linking oxidative stress and female infertility. Biomed Res Int. 2014.

77. Greiner M, Paredes A, Araya V, Lara HE. Role of stress and sympathetic innervation in the development of polycystic ovary syndrome. Endocrine. 2005; 28: 319-324.

78. Holte J, Bergh T, Berne C, Wide L, Lithell H. Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1995; 80: 2586-2593.

79. Grulet H, Hecart AC, Delemer B et al. Roles of LH and insulin resistance in lean and obese polycystic ovary syndrome. Clin Endocrinol. 1993; 38: 621-626.

80. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update. 2010; 16: 347-363.

81. Pasquali R and Gambineri A. Metabolic effects of obesity on reproduction. Reprod Biomed Online. 2006; 12: 542-551.

82. Pelusi B, Gambineri A, Pasquali R. Type 2 diabetes and the polycystic ovary syndrome. Min Gynecol. 2004; 56: 41-51.

83. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diab Care. 1999; 22: 141-146.

84. Peppard HR, Marfori J, Iuorno MJ, Nestler JE. Prevalence of polycystic ovary syndrome among premenopausal women with type 2 diabetes. Diab Care. 2001; 24: 1050-1052.

85. Block MS, Maurer MJ, Goergen K, et al. Plasma immune analytes in patients with epithelial ovarian cancer. Cytokine. 2015; 73: 108-113.

86. Majumdar A and Singh TA. Comparison of clinical features and health

manifestation in lean *vs*. obase Indian women with polycystic ovary syndrom. J Reprod Hum Sci. 2009; 2: 12-17.

87. Yudkin JS, Stehouwer C, Emeis J, Coppack S. C-reactive protein in healthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction. Arterioscle Thromb Vasc Biol. 1999; 19: 972-978.

88. Engstrom G, Hedblad B, Stavenow L, et al. Inflammation-sensitive plasma proteins are associated with future weight gain. Diabetes. 2003; 52: 2097-2101.

89. Carmina E. Obesity, adipokines and metabolic syndrome in polycystic ovary syndrome. Front Horm Res. 2013; 40: 40-50.

90. Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low- grade chronic inflammation in polycystic ovary syndrome. Reproduction. 2015; 149: 219-227.

91. Faloia E, Canibus P, Gatti C et al. Body composition, fat distribution and metabolic characteristics in lean and obese women with polycystic ovary syndrome. J Endocrinol Invest. 2004; 27: 424-429.

92. Kiddy DS, Sharp PS, White DM et al. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: An analysis of 263 consecutive cases. Clin Endocrinol. 1990; 32: 213-220.

93. Pasquali RE, Cantobelli ST, Casimirri FR. The hypothalamic-pituitary-adrenal axis in obese women with different patterns of body fat distribution. J Clin Endocrinol Metab. 1993; 77: 341-346.

94. Toulis KA, Goulis DG, Farmakiotis D, et al. Adiponectin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis. Hum Reprod Update. 2009; 15: 297-307.

95. Mirza SS, Shafique K, Shaikh AR, Khan NA, Qureshi MA. Association between circulating adiponectin levels and polycystic ovarian syndrome. J Ova Res. 2014; 7: 18-24.

96. Teede HJ, Misso ML, Deeks AA, et al. Assessment and management of polycystic ovary syndrome: Summary of an evidence-based guideline. Med J Aust. 2011; 195: 65-112.

97. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US children, 1989–1991. Pediatrics. 1998; 102: 913-923.

98. Bowman SA, Vinyard BT. Fast food consumption of US adults: Impact on energy and nutrient intakes and overweight status. J Am Coll Nutr. 2004; 23: 163-168.

99. Bowman SA, Gortmaker SL, Ebbeling CB, Pereira MA, Ludwig DS. Effects of fast-food consumption on energy intake and diet quality among children in a national household survey. Pediatrics. 2004; 113: 112-118.

100. Jeffery RW, Baxter J, McGuire M, Linde J. Are fast food restaurants an environmental risk factor for obesity? Int J Behav Nutr Phys Act. 2006; 3: 2-7.

101. Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, et al. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. J Clin Endocr Metab. 2007; 92: 2500-2505.

102. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2011.

103. Panidis D, Tziomalos K, Papadakis E, et al. Lifestyle intervention and anti-obesity therapies in the polycystic ovary syndrome: Impact on metabolism and fertility. Endocrine. 2013; 44: 583-590.

104. Elmenim SOA, Emam AMM. Effect of lifestyle changes on symptoms of polycystic ovarian syndrome in obese girls. IOSR J Nurs Health Sci. 2016; 5: 1-10.

105. Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. TRENDS Endocrinol Metab. 2002; 13: 251-257.

106. Vause TD, Cheung AP, Sierra S. Ovulation induction in polycystic ovary syndrome. J Obst Gynaecol Can. 2010; 32: 495-502.

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