

Review

Polycystic ovarian syndrome: Environmental/occupational, life style factors-an overview

Kshetrimayum et al. PCOS and occupational/environmental factors

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ABSTRACT

PCOS is a multifaceted disease in women with infertility that have diverse etiological factors. Some women may have only a few PCOS linked symptoms or mild symptoms while some of the women will have severe or all PCOS linked symptoms. Therefore, the PCOS symptoms can differ among the woman. PCOS is a state of hormonal imbalance, excess terminal hair (hirsutism), hair loss (alopecia), menstruation impairments, metabolic disorders and cysts appearance on the ovaries. The cysts hamper ovulation, thus reducing the ability of women to become pregnant and resulted into infertility.

The data available suggests that PCOS might be originated in utero and phenotypic appearance of PCOS symptoms may be developed at later life which could be linked with host factors (endogenous and exogenous), lifestyle, and dietary, environmental or occupational factors etc.

Based upon the available information, it can be postulated that prenatal exposure to excessive androgen might be responsible for androgenization of the fetus which in turn may alter the program of differentiating target tissues and the phenotypic characters of PCOS can be persuaded by exposure of female child to various endogenous and exogenous factors at later life. Genetic/host and environmental/lifestyle factors might be related to the pathophysiology of PCOS after prenatal exposure to androgen. Additional studies are necessary to understand the exact mechanism responsible for the manifestation of PCOS as it is a very important issue in female reproduction.

Keywords: PCOS; Environmental; Occupational; Hyperandrogenism; Anovulation; Genetic factors; Androgenization; Infertility.

Introduction

Polycystic ovary syndrome (PCOS) is a problem of teen girls or women in which their hormonal levels are impaired. It can cause problems in the menstruation cycle and difficulty to conceive. In this disease, many small cysts are developed in the ovaries of women; hence it is called as polycystic ovary syndrome. PCOS is globally, considered to be the foremost reason for infertility in women including India. PCOS is a multifaceted disease having various etiological factors, which might be related with the disease or exaggerate the problem or induces PCOS phenotypic characteristic in women at adulthood. Owing to anovulation in women it is the main cause of infertility and most common endocrine disorder of women. It affects the lives of women from *in utero* life to till death, PCOS is also linked with several other health hazards which in turn elevate morbidity, impair quality of life and increases mortality rate etc. (1). The prevalence of PCOS differs as several diverse criteria are used for the diagnosis of PCOS by different investigators and diverse norms for diagnosis are also suggested by various organizations. It is an endocrine syndrome with menstruation irregularities, hyperandrogenism, and polycystic ovaries of women (2). Based upon the criteria of diagnosis for PCOS by European Society for Human Reproduction & Embryology/American Society for Reproductive Medicine, the prevalence of PCOS is about 15-20 % (2). Later, a meta-analysis was conducted by including studies which were published from 2006 to 2011 from Iran. The prevalence rate based on the criteria of National institute of child health and human disease of U.S. was 6.8%, 19.5% based on Rotterdam norms, and 4.4% based on ultrasound criteria (3). About 5 to 10% of reproductive-aged women of Indian sub-continent are reported to be affected with PCOS. Polycystic ovaries, chronic anovulation, and hyperandrogenism are the distinctive characteristics of PCOS and with the existence of insulin resistance, hyperinsulinemia, hypertension, abdominal obesity, and dyslipidemia are responsible for long-term serious outcomes such as endometrial hyperplasia, type 2 diabetes mellitus, and coronary artery disease (4). They also mentioned that it is only the interaction of environmental factors (obesity) with the

genetic factors that result in the appearance of PCOS, even though a woman may be genetically susceptible for the development of PCOS (4).

Many women may have PCOS illness and live without being diagnosed clinically. March et al. (2010) draw attention on this important issue of PCOS diagnosis in the community and mentioned that about 68 % women having PCOS, which were not diagnosed for PCOS in past (5). This showed the seriousness of the diagnostic problem of PCOS in the community. Further, the appearance of PCOS may also affect the mental health of the subjects that might also be related to psychiatric problems among them due to difficulty to get conceived. The prevalence of depression and anxiety was 27.5 and 13.3% % respectively in PCOS subjects as compared to 3.0 and 2.0 % depression and anxiety respectively among control subjects (6). Further, about 65–70% of women suffering from PCOS were having compensatory hyperinsulinemia and insulin resistance (7). In addition, an inherent ovarian defect (possibly genetically) being existed in PCOS women that make the ovary vulnerable to insulin stimulation of androgen production. However, a limited data/evidence also suggests hyperinsulinemia might stimulate androgen production in ovaries (8). Later, Baptiste et al. (2010) mentioned several steps for the appearances of PCOS a) Enzymatic default in the ovarian and/or adrenal steroidogenesis; b) Variation in the gonadotropin-releasing hormone that encourages luteal hormone secretion; or c) Amendments in insulin actions leading to insulin resistance with compensatory hyperinsulinemia. Some women with the characteristic of PCOS do not show insulin resistance, this advocates the hypothesis of genetic predisposition to PCOS. This would be exhibited by the progression of insulin resistance and compensatory hyperinsulinemia in the majority of the women with PCOS, but not all PCOS women (9).

In addition to the endogenous or host factors, it is also recognized that some factors like chemical, physical, dietary, lifestyles, occupational and environmental factors are accountable for hostile consequence on human male and female reproduction and they might also affect pregnancy and its outcome. Several reports and reviews on the role of occupational and environmental aspects on different aspects of human reproduction (10,11,12, 13, 14) and controlled experimental studies on certain environmental and lifestyle factors on reproductive health are published (15, 16, 17) from this laboratory.

The hazard factors of PCOS comprised menstrual cycle impairment (OR = 5.8), bad mood (OR = 2.8), diabetes history in family (OR = 7.0), infertility in family (OR = 11.9), mother menstrual irregularity (OR = 2.5) and physical exercise deficiency (OR = 1.8) (18). The existing data on various environmental factors suggest their potential contribution in the etiology, prevalence, and modulation of the syndrome. There are evidences which advocated that environmental factors might play a significant role in deteriorating reproductive health and some environmental factors are vital behind the deterioration, includes environmental toxins, diet and nutrition, socioeconomic status, and geography (19), still research/data on these environmental factors with reference to the causation of PCOS are limited or inconsistent and need further well-planned studies.

This overview is furnished based on available information on the role of occupational, environmental, lifestyle factors in PCOS. The information was collected through searching various websites such as Google, Pub Med, Medline, Toxline, and other websites and consulting related books. This overview is separated into various segments and the first section deals with the existing information on the recognized host/genetic factors associated with PCOS. The second and third section deals with occupational/chemical exposures and lifestyle factors that might be associated with PCOS. In addition, some light on oxidative stress in the occurrence of PCOS is also furnished. The majority of on-hand reviews on PCOS are available on the host/genetic factors rather than the role of both occupational/ environmental toxicants exposure and lifestyle influences and PCOS. In this review, importance has been given on parental environmental exposure, lifestyles factors in PCOS covering mainly human studies. The possible etiological factors related to progression/development of PCOS are depicted in figure -1.

Results and Discussion

The exact mechanism for the manifestation of PCOS is not yet completely understood; the syndrome appears to involve genetic, environmental, dietary, metabolic components etc. The origin of PCOS started from early life in mother womb which extended throughout the lifecycle, environmental insults and lifestyle issues may affect vulnerable women leading to the occurrence of phenotypic characteristics of PCOS. Diet seems to be one of the foremost environmental determinants for the occurrence of PCOS. The hormone levels are an imbalance among PCOS's women. Generally, PCOS women have elevated male hormone (androgens) and lower levels of the female hormone (estrogen). High androgen level can also have a significant impact on female reproductive development and functions. PCOS seems to be one of the ancient ailments that continued through human evolution (20). There is a report which indicated that anti-mullerian hormone (AMH) was 2-3 three times higher in PCOS women as compared to the normal level (10 ± 2.2 ng/mL) and this high AMH level is a good indicator of infertility and PCOS (21). Further, PCOS women are stated to have significantly higher levels of serum AMH as compared to control and the occurrence of negative and positive correlations with other hormonal parameters showed involvement of AMH at least in part in the manifestation and development of PCOS (22). The data available on serum level of AMH in subjects with PCOS suggests its use as a diagnostic biomarker and it can

serve as a reliable tool to describe the severity of the disorder, monitoring, forecasting and prognosis of the diseases etc.

Recently it has been stated that AMH is raised and linked well with the several reproductive, metabolic and endocrine impairments in subjects with PCOS. The AMH also has an inhibitory function in follicular growth and recruitment. The FSH-induced aromatase production due to preventive action of AMH probably contributes to hyperandrogenism that further increases the insulin resistance in PCOS women. In addition, elevation in serum AMH levels is extrapolative of poor treatments response in PCOS women i.e., loss of weight, induction of ovulation and laparoscopic ovarian drilling, whereas improvement in several other clinical parameters after treatment was related to declining serum AMH level. This advocates a significant role of this hormone in the pathophysiology of PCOS (23). The pregnancy-related difficulties were reported to be more in PCOS women. Various etiological factors involved in PCOS and allied co-morbidities may also be connected to compromised pregnancy and/or its outcomes. A possible relationship between genetic, environmental, clinical and biochemical, dietary factors is involved in the occurrence of this complex syndrome, with pregnancy complications and its outcome (24). In this overview, more emphasis has been given on lifestyle, occupational, environmental issues and PCOS. However, some information on other factors is also incorporated to understand the overall possible causative factors/mechanism connected with PCOS.

Endogenous/host/genetic factors

Several genetic / hosts factors might be related to the development/occurrence of PCOS. The genetics behind the appearance of PCOS is yet not fully understood but provided ample evidence of their role in PCOS. Further, a considerably higher number of women in PCOS group was reported with the family history of diabetes and some women in this group also had self-history of diabetes. Whereas no women were diabetic in the controls (25). The menace of type 2 diabetes is noticeably higher in PCOS middle-aged women which suggest that BMI, glucose, sex hormone binding globulin levels are connected to the risk stratification of PCOS (26). Based upon the animal studies and reinforced by clinical studies, it is reported that PCOS has its origin in fetal life and, exposure to excess androgen since the time of growth of ovary at fetal life, to the commencement of puberty, leads to distinctive features of PCOS, along with irregularities in luteinizing hormone secretion and insulin resistance (27). PCOS is raised from the ancestral gene variants which are an ancient syndrome. Such ancient genes were likely to be transmitted trans-generationally through offspring conceived amongst fertile carrier males and sub-fertile affected females (20). PCOS is a heterogeneous syndrome and commonly determined by the implication of two vital factors i.e., hyperandrogenism and insulin resistance (28). Alterations in genes that control the ovarian steroidogenesis are possibly the foremost contributing factor of hyperandrogenism. Insulin resistance may be due to different gene variations such as insulin receptor substrate (IRS)-1 and 2, calpain-10 and peroxisome proliferator-activated receptor. In most subjects, PCOS seems to be determined by the association of gene polymorphisms, common in the general population but gene polymorphisms alone are incapable to determine the phenotypic consequences. The heterogeneity of the ailment can be explained by numerous combinations of multiple gene polymorphisms and environmental factors (28). Based upon numerous available studies; a sturdy genetic element is evident for the etiology of PCOS. Keeping in view to the vast genetic and phenotypic heterogeneity of PCOS and inadequate large cohort's studies to identify precise causative genes, only a few definite outcomes were provided that concluded heterogeneity of disease and inadequate sample sizes complicated the identification of exact genes responsible for PCOS (29). The heritable predispositions have been stated in the occurrence of PCOS, and genome-wide association study (GWAS) regarding PCOS showed evidences for the genetic mechanisms in PCOS pathophysiology. They suggested that studies using innovative techniques such as next-generation sequencing would be beneficial to understand more about underlying variants for PCOS (30). Further, PCOS is reported to be linked with oligomenorrhea, hirsutism, hyperandrogenism, insulin resistance, obesity, and hazard of type 2 diabetes mellitus ~ 7-folds (31). Most of the PCOS women (both obese and lean) have insulin resistance. The minisatellite of the insulin gene, specifically class III alleles and III/III genotypes are connected to the risk of type 2 diabetes and determine the predisposition to anovulatory PCOS. In addition, the appearance of estrogen receptor and 5-alpha-reductase genes (SRD5A1-2 genes) activity in granulosa and theca cells indicated a significant variation in the expression of ER alpha and ER beta in PCOS that may be linked with anomalous follicular development (31). The higher frequency of individuals with PCOS and extensive range of phenotypic appearance of the disease can be elucidated by the interaction of several main genes with environmental factors (32). Although some confirmation of familial segregation and clustering of the ailment in the first-degree relative of PCOS women has been demonstrated, with no pattern of inheritance. The existing genetic studies put forward a strong familial element and PCOS is considered a polygenic trait which might be a consequence of the interaction of vulnerable and defensive genomic variants and environmental aspects, during pre or postnatal life (32). Based upon all these studies, it can be inferred that PCOS has a sturdy genetic element in the occurrence of this syndrome along with other factors.

Dunif and Thomas (2001) mentioned that family history showed a genetic vulnerability of PCOS (33). PCOS women with insulin resistance have ~ 50 % chances of their sister with polycystic ovaries; hyperandrogenemia

and high low-density lipoprotein are consistent with genetic traits. Family-based studies on linkage and association of factors have implicated numerous genes in the causation of PCOS (33). Further, it is apparent that Genome-wide association studies have evolved powerful means for studying the genetic architecture of human disease (34). PCOS declines fertility without changing in prevalence and it was considered as an evolutionary paradox (35). Overall 17 single nucleotide polymorphisms (SNPs) were identified by GWAS studies which are related to PCOS, with different allele frequencies, ethnicity-related, in 11 susceptible loci. They further examined phenotype-genotype correlations of PCOS *in silico* and suggested that PCOS is a genetic gradient resulted from genetic drift due to a serial consequence took place in early human migrations (35). A few GWAS studies were published on PCOS from diverse areas and different ethnic groups of the world i.e. European countries, China, Korea, etc. AGWAS study on PCOS was carried out among Han Chinese and acknowledged sturdy evidence of an association between PCOS and three loci: 2p16.3; 2p21 and 9q33.3. These results offer new understanding of the pathogenesis of PCOS (36).

Lee et al. (2015) recognized, novel locus with genome-wide implication and seven moderately linked loci in Korean PCOS women. The strongest relationship was found on chromosome 8q24.2, and other association signals were situated at 4q35.2, 16p13.3, 4p12, 3q26.33, 9q21.32, 11p13 and 1p22. The sturdiest signal was situated at upstream of KHDRBS3, that is linked with telomerase activity, and that might be resulted to PCOS and associated phenotypes (37). Later, common genetically susceptible loci were also reported in European lineage women and three loci were reported to have genome-wide implication in the case control meta-analysis i.e. two novel loci mapping chr 8p23.1 and chr 11p14.1, and a chr 9q22.32 locus found earlier in Chinese PCOS women also. PCOS diagnosis and LH levels were strongly linked with the chr 11p14.1 SNP, rs11031006, in the region of the follicle-stimulating hormone B polypeptide gene (38). The genetic risk calculated by GWAS studies was significantly connected with PCOS and associated clinical features (39). There is a report which indicated that androgen metabolism is deteriorated in PCOS women and, thus, the CYP19 gene which is associated in this pathway can be a novel gene for investigation (40). Studies also revealed an association between single nucleotide polymorphism (SNP) of the CYP19 gene in hyperandrogenism and PCOS in some ethnic groups. They further stated that among Iranian women, variants of SNP rs.2414096 in CYP19 could be responsible in the occurrence of PCOS (40). All these studies clearly suggest the role of genetical factor in the appearance of PCOS.

Environmental/Occupational factors

Exposure to some of lifestyle, occupational, environmental factors may enhance the elevation in the occurrence of PCOS or exaggerate the incidence of PCOS and/or phenotypic signs of PCOS but cause effects relationship of these aspects with PCOS is still lacking or inadequate. There are also inadequate or inconsistent studies on exposure to environmental/occupational/lifestyles factors with regards to PCOS. Further, women are exposed to several chemicals during their day to day activity without their knowledge and some of these chemicals may have estrogenic or anti-estrogenic, androgenic or anti-androgenic properties and these chemicals act at a very low dose and known as endocrine disruptor. The endocrine disruptors (EDs) might act through membrane-bound estrogen-receptors, estrogen-related receptors, nuclear receptors, interaction with targets in the cytosol and variations in endogenous hormones metabolism, cross-talk between genomic and non-genomic pathways, interfering with feedback regulation, cross-talk with estrogen receptors after binding on other receptors and alterations in neuroendocrine cells, DNA methylation or histone alterations (41). There is a report which indicated that experimental exposure to industrial endocrine disruptive chemicals contributed to the worsening of normal reproductive function and metabolic regulation, perhaps contribute to the growth of or enhancing PCOS-resembling clinical ailments. Industrial chemicals may also contribute to the causative role of a hostile environment to unveil PCOS characteristics in genetically susceptible individuals or further deteriorate the hormonal steadiness and fertility status of women with PCOS (42).

In addition, hormonal activity is affected due to exposure to chemicals in the womb may exaggerate the growth of PCOS. The elevated concentrations of bisphenol A (BPA) in PCOS women and a noteworthy positive relationship between androgens and BPA suggests a probable role of this endocrine disruptor in the causation of PCOS (43). Further, elevated serum bisphenol-A level was found in teenage girls with PCOS, independent of obesity more than the controls. Bisphenol-A level was also evidently associated with androgen concentration, leading to infer that bisphenol-A may have a considerable role in the occurrence of PCOS in teenage girls (44). Exposure to EDs during prenatal development that mimics natural hormones might contribute to deviate the fetal programming of target tissues which may be associated to PCOS and may have several potentially adverse trans-generational health effects (45). Chronic or acute exposure to advanced glycation end products and EDs during various stages of life cycle may arise in interruption of hormonal homeostasis that linked to the deterioration of reproductive functions. They may also interfere with metabolic changes like insulin resistance, obesity, and compensatory hyperinsulinemia which can contribute to PCOS consequences like cardiovascular disease and type-2diabetes (45). However, phthalic acid esters, bisphenol-A and octylphenol do not induce an apparent effect on the manifestation of PCOS or contribute to insulin resistance, but octylphenol may play a considerable role in insulin resistance in PCOS subjects (46).

Vagi et al. (2014) also conveyed that PCOS subjects might have different environmental contaminant profile from controls and reported that PCOS women had higher serum concentrations of perfluoro ctanoate-PFOA and perfluoro octane sulfonate-PFOS, and lower concentrations of mono-n-butyl phthalate and mono-benzyl phthalate in urine. They also mentioned that more studies are required to confirm these findings (47). The environmental factors are likely to be related with the occurrence of PCOS. The PCOS women were found to be more common in consuming plastic-packaged food, eating fruit with pericarp, pesticide exposure, staying close to a garbage heap, working at an acid plant, taking Chinese medicines, smoking and ingesting alcohol than controls. Eating plastic-packaged food, eating fruit with pericarp and alcohol consumption were independent hazards for the manifestation of PCOS (48). They further reported that relationships of these factors with PCOS should be confirmed by conducting additional studies. Earlier it was also reported that environmental issues linked to PCOS were occupation, education, disposable drinking plastic cup, indoor decoration, and cooking oil fume and all were significantly connected to PCOS (49). It is recognized that PCOS has the characteristic of endocrine disturbances, thus EDCs might be one of the underlying causes of PCOS. Based upon experimental studies, it was stated that BPA exposure in the perinatal stage, often at doses comparable to human exposure interrupts ovarian and reproductive function. Bisphenol-A seems to have obesogenic qualities, affecting standard metabolic function and the body becomes prone to overweight. Cross-sectional studies suggested that PCOS women have higher BPA levels with respect to women with good reproductive health. They also suggested that additional investigations are required to extrapolate the mechanisms wherein EDs might be linked with PCOS and critical time periods of EDCs exposure that may have a trans-generational effect (50). Recently, the relationship between PCOS and anogenital distance (AGD) was explored by different investigators which are a biomarker of androgen exposure in fetal development and observed that PCOS subjects exhibited higher AGD as compared to control. This infers that PCOS has an intrauterine origin, and fetal hormonal environment may be responsible for the advancement of PCOS in later life (51). It is acknowledged through animal studies that, prenatal exposure to high testosterone induces PCOS-like phenotypes, even though etiology of PCOS is unfamiliar. Further, hypothesis i.e. infant girls born to PCOS women have longer AGD that implies excess prenatal testosterone exposure with respect to girls born to women without PCOS. They found that AGD was longer in the daughters of PCOS women with respect to the daughters of women without PCOS (52). The prevailing information on prenatal exposure to three important categories of EDCs i.e. phthalates, bisphenol-A, androgenic EDCs and the occurrence of PCOS and/or PCOS-linked anomalies were described that 1) maternal BPA exposure modifies sexual maturation and postnatal development in rodents, 2) gestational exposure to dibutyl phthalate and di-(2-ethylhexyl) phthalate induces polycystic ovaries and PCOS like hormonal profile 3) androgenic EDCs like 3,4,4'-trichlorocarbaniide and nicotine, generate fetal hyperandrogenic environment. They concluded that EDCs exposure during prenatal growth may be accountable to alter fetal programming (53).

Lifestyles and dietary factors

Lifestyles and dietary factors can be indirectly contributing to the occurrence of PCOS as exposures to these factors are linked with the appearance of PCOS in girls who are susceptible to PCOS. PCOS is a common ailment, and PCOS women have reproductive, metabolic and psychological consequences. Weight gain and obesity deteriorate the characteristic features of PCOS, while weight decline, diminishes the characteristic features of PCOS (54). The excess weight loss through lifestyle alteration leads to menstrual regulation and regulates reproductive outcomes women with PCOS. The available data support that a moderate diet in carbohydrates, poly and mono-unsaturated fats, and high content of fiber with lean protein sources, are beneficial to overall health parameters in women having PCOS. Further, incorporation of exercise in daily life showed a positive effect on the clinical representations of PCOS (55). Therefore, management of PCOS must include better lifestyle approaches for example proper diet, exercise, optimization of body weight and improving insulin sensitivity, to target the PCOS-related health apprehensions. Recently, the lifestyle (diet and exercise) intervention was shown to recover levels of FSH, SHBG, androstenedione, total testosterone, free androgen index, and Ferriman-Gallwey score in PCOS women (56). Losing body weight and exercise are important factors which reported to improve the condition of menstrual impairment and infertility was noticed in obese PCOS women (57). The lifestyle variation program with importance on behavioral management, dietary and workout interventions have been described to be successful in lowering the hazard of diabetes, the metabolic syndrome in the general population and accomplishment in improving fertility outcomes in PCOS patients (58). These data clearly exhibited the positive role of adopting a healthy lifestyle for the managing of PCOS to some extent.

Trace and heavy metals in PCOS women

Some metals in trace quantity are essential for various physiological functions in the human body. Hence these are called essential trace metals. The essential trace and heavy metals were studied in human PCOS subjects and serum copper (Cu), and zinc (Zn) levels were found to be significantly higher while manganese (Mn) and lead (Pb) levels were lower in PCOS subjects. These findings should be explored further to find new insights into

metals and PCOS (59). Further, no considerable differences in the median levels of barium, lead, cadmium, chromium, arsenic, strontium, gallium, and vanadium were reported amongst PCOS and the control subjects. Whereas serum nickel and copper concentration were significantly higher, while zinc was significantly lower in subjects with PCOS in comparison to control. Thus, the metal such as copper, and nickel might be implicated in the causation of PCOS and linked with impairment of reproductive hormone levels (60). Relationship between hormonal impairments and the alterations of trace element (manganese), macro elements (magnesium and calcium), heavy metals such as cadmium and lead in both Obese and Non-Obese PCOS subjects was studied and significantly higher blood Pb and Cd levels were found in PCOS subjects (Non-Obese and Obese) as compared to control subjects while significantly low level of magnesium, calcium, and manganese were recorded in PCOS subjects (61). The serum FSH level was lower significantly in obese PCOS subjects compared to control (obese and non-obese) subjects. A positive association was observed among serum testosterone and Cd levels in obese PCOS women. This study has established that elevated blood Pb and Cd concentrations and lower levels of serum calcium, magnesium, and manganese were observed in PCOS subjects as compared to control (61). Later Taher and Mahibes (2017) reported that serum copper and nickel levels were considerably elevated in PCOS subjects, while the concentration of serum zinc was declined in PCOS subjects (obese and non-obese) in comparison to controls (obese and non-obese) (62). Further, Sedighi et al. (2015) has compared the lifestyle of PCOS women and reported a noteworthy association between the manifestation of PCOS and improper diet, low physical activity, but no association between PCOS and unhealthy behaviors (63). The data on lifestyle, dietary and some metals suggests that these factors may also have some role in the occurrence of PCOS phenotypic symptoms and weight management, healthy lifestyle, regular exercise might be beneficial in reduction of PCOS linked features in young adult girls.

Oxidative stress and PCOS

In addition to androgenization of female fetus, genetics, host, dietary and other environmental, lifestyle factors etc., oxidative stress might also be related in the occurrence of PCOS. Oxidative stress is a phenomenon of disproportion between the excessive generation of free radicals and the balancing system of antioxidant status in the body to detoxify these extra free radicals efficiently. Based upon a review on oxidative stress indicators in PCOS women, it was mentioned that circulating indicators of OS are unbalanced in PCOS women independent of excess weight suggesting that OS might play a significant role in the occurrence of PCOS (64). An increased level of ROS and myeloperoxidase in subjects with insulin resistance (IR) and PCOS were also reported. Further, inflammation in PCOS subjects brings leukocyte-endothelium interactions and a concurrent elevation of TNF- α , IL-6, leukocytes, and adhesion molecules i.e. E-selectin, ICAM-1 and VCAM-1 and these situations are heightened by the existence of insulin resistance (65). Further, OS is a significant factor of the cardio-metabolic hazard found in PCOS women and adjusting oxidative stress with supplementation of antioxidants along with measuring of antioxidant status could have a valuable effect on OS-induced hyperandrogenism and insulin resistance found in PCOS non-obese women (66).

Earlier, González et al. (2006) reported that ROS production in response to hyperglycemia from mononuclear cells is elevated in PCOS subjects which are independent of obesity. The resultant OS might subscribe to a proinflammatory state which persuades hyperandrogenism and insulin resistance in PCOS women (67). In addition to hormonal imbalances, defects in insulin signaling and dysfunction of adipose tissue, oxidative stress, has been sturdily implicated in the etiology of occurrence of the PCOS. Oxidative stress, with other etiological factors of PCOS and involvement of environmental factors, leads to a hostile redox status that stigmatizes the normal progression of the PCOS (68). The strong association of insulin resistance with OS at the visceral adipose tissue level was also observed indicating local OS and defects of insulin signaling in adipose tissue may play a vital role in the causation of PCOS (69) along with other genetic, host and dietary or environmental factors.

The program of differentiating target tissues to the occurrence of PCOS phenotypic characteristic later in life might be resulted from the prenatal androgenization of the female fetus resulted due to both genetic and environmental factors, and their interaction (70). The data available from both experimental and clinical studies suggested that maternal hyperandrogenism is a causative factor of PCOS, and variations in the gestational endocrine environment due to hyperandrogenism in PCOS women in pregnancy, may play a vital part in the vertical transmission of PCOS. They emphasized the scanty data on human at early gestational stages and the importance of experimental data to understand the cellular and molecular mechanisms involved in the programming of adult diseases and proposed a two-hit hypothesis for the appearance of PCOS i.e. perinatal organizational and postnatal activation events (71).

Based upon available clinical and experimental data, one can infer that PCOS is a consequence of androgenization as well as alteration of program of target tissues differentiation during fetal development, metabolic disorders and exposure to EDs during pre and postnatal development along with lifestyle and dietary factors in later life are associated with development of PCOS phenotypic symptoms and this also support the two-hit hypothesis i.e. prenatal organizational and post-natal activation as reported earlier (71). The

management of PCOS can be achieved through better lifestyles such as appropriate diet, exercise, optimization of body weight, improving insulin sensitivity to control this syndrome.

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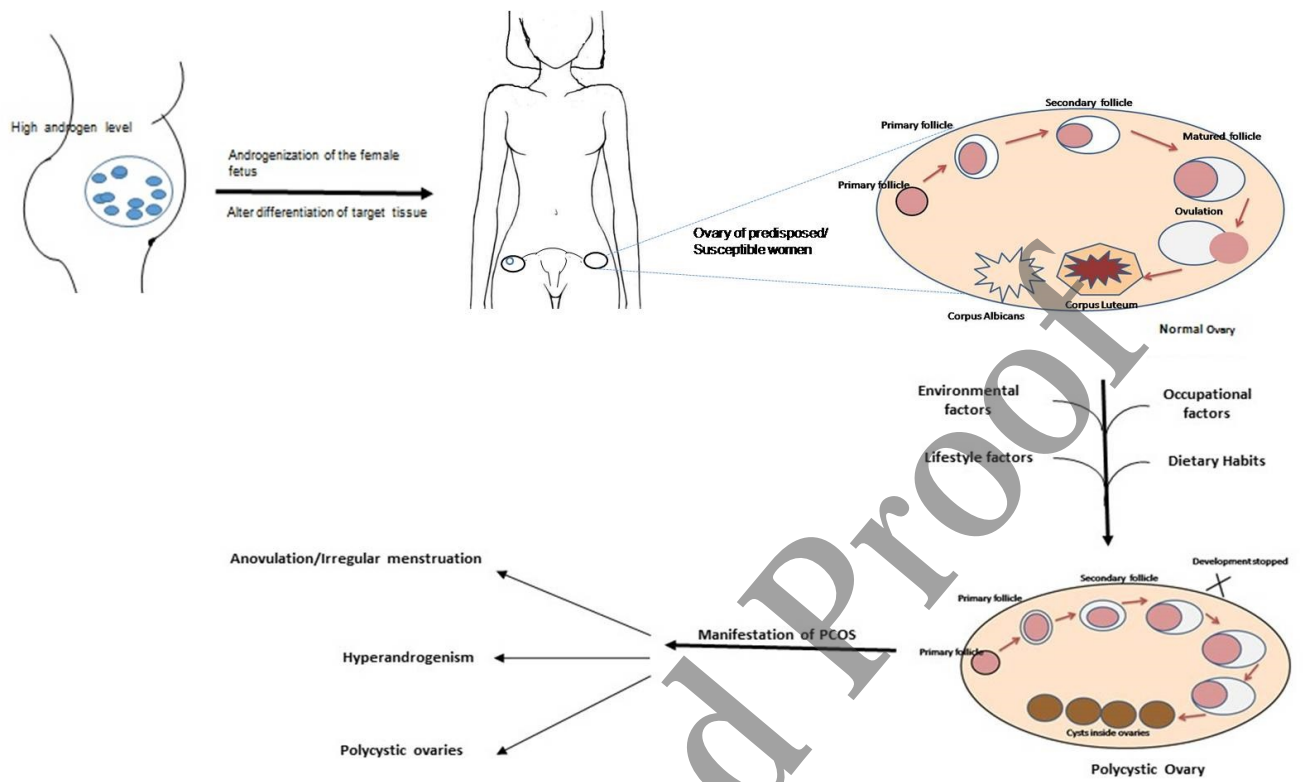


Figure 1: Possible factors of occurrence of PCOS