POLYCYSTIC OVARIAN SYNDROME (PCOS): A LIFESTYLE UPSHOT AND CLUSTER OF MALADIES

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Abstract. Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that distresses millions of females all over the world during their procreative age of 18–44 years. This syndrome leads to the complexities such as numerous cysts, and an irregular menstrual cycle eventually manifesting in infertility. Complications like insulin resistance and cardiovascular disease are also associated. Several studies have confirmed the genetic basis of PCOS by identifying many candidate genes. Thus, PCOS is a multigenic, multifactorial, deregulated steroid state with a systemic inflammatory autoimmune disease manifesting predominantly due to lifestyle fallacies. Diagnosis of PCOS is through ultrasound scanning and biochemical analysis. Medications include oral contraceptive pills, metformin, and hormones which will bypass or reverse the ill effects of PCOS. However, lifestyle correction to prevent aberrant immune activation and minimized exposure to inflammatory agents appears to be a sustainable therapy. This review primarily aims to understand the various aspects of PCOS viz., the pathophysiology of irregularity of gonadotropin-releasing hormone (GnRH), anomalies in leptin-adiponectin and oxidative stress, genetic and molecular causes (candidate gene associated), environmental factors, metabolic factors, and a role of the irregular circadian rhythm. Prevailing treatment recommends a multicomponent diet and a healthy lifestyle to manage PCOS and avoid its comorbidities.
Keywords: *amenorrhea, endocrine disorder, hyperandrogenism, hyperprolactinemia, infertility*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting reproductive-aged women. One in every 5-6 females is facing serious complications regarding infertility and irregularity in their menstrual cycles. It is a loop of various disorders resulting in the disruption of normal reproductive function resulting in the irregularity of the menstrual cycle and absence of ovulation leading to infertility (Ajmal et al., 2019; Bhalerao and Aranha, 2021). Stress, obesity, and fluctuation in hormonal levels are the major cause worldwide. Gynecologists Irving F Stein, SR, and Michael L. Leventhal called this condition Schlerocystic Ovaries, Multicystic ovaries, and Stein Leventhal Syndrome. Clinically PCOS is diagnosed using Rotterdam criteria that consider polycystic ovarian morphology, hyperandrogenism, and oligomenorrhoea. The etiology of PCOS is credited to an imbalance of female reproductive hormones estrogen and progesterone. Hormonal imbalance due to metabolic disturbances in gonadal steroid hormone synthesis affects normal reproductive physiology as depicted in *Figure 1*. The lack of appropriate levels of female sex hormones causes uterine and ovarian dysfunction viz., anovulation, oligoovulation, and polycystic ovarian morphology. Generally, the surge of LH hormone mediates a series of molecular and biochemical changes triggering a release of a mature egg. Despite excessive LH in PCOS ovulation is affected resulting in the accumulation of several antral follicles with mature eggs in the ovary termed polycystic ovaries leading to a disrupted menstrual cycle (Bhalerao and Aranha, 2021).

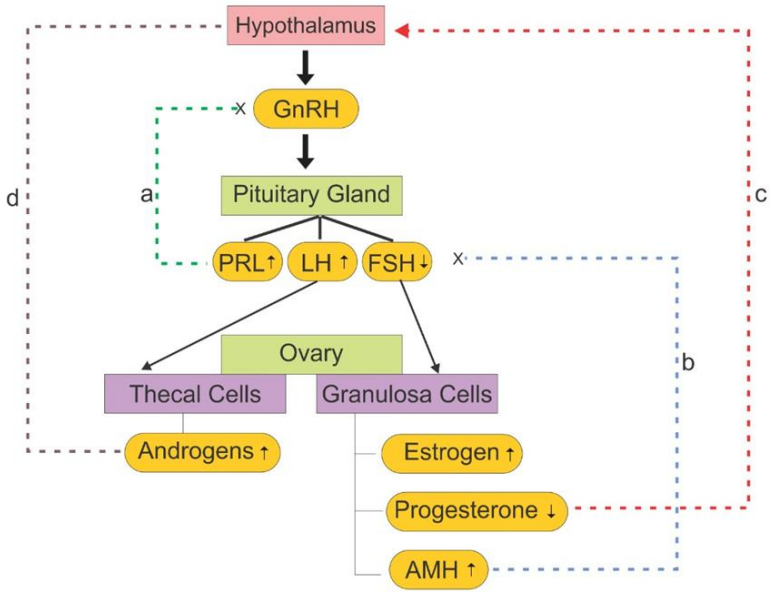

Figure 1. *Depiction of pathophysiology of polycystic ovary syndrome: (a) Increased PRL inhibits the GnRH levels; (b) Increased AMH levels show an inhibitory effect on FSH levels; (c) Decreased Progesterone levels stimulate Hypothalamus for secretion of GnRH; (d) Increased Androgens affect the neurophysiology of PCOS females.*

The female reproductive physiology is nurtured and maintained by optimal levels of female sex hormones. When these hormones are at a suboptimal level the reproductive system bared to male sex hormones androgens (Testosterone and Dihydro epiandro stenedione, DHEA) in excess. As a result, the basic cellular metabolism is reprogrammed affecting the responsiveness of the target tissue of estrogen and progesterone hormone. Considering the differences in hormonal levels phenotypic feminine traits recess and masculine traits like increased facial hair near the upper lip and lower chin (hirsutism) and male patterned baldness are noted (Bhalerao and Aranha, 2021). Also increased facial acne, oily skin, and hyperpigmentation are eminent in this situation. Apart from the effects on reproductive physiology, neuronal health will also get compromised producing anxiety, depression, insomnia, and sleep apnea. PCOS leads to several other acute disorders such as insulin resistance (IR), increased risk of type 2 diabetes mellitus, obesity, cardiovascular disorders, dyslipidemia, hepatic steatosis, and endometrial carcinoma (Patel, 2018). Unhealthy lifestyle practices are a perfect boost for increasing the severity of these metabolic disturbances. Even though the hormonal imbalance can be restored back by medications but the long-term effects mentioned can persist lifelong damaging the quality of life. The sternness of PCOS can only be reduced through appropriate preventive measures viz., weight loss, healthy diet, healthy lifestyle, and recommended medications. This review comprehends in detail the updated investigations on various aspects of PCOS to highlight its magnitude.

Discussion

Pathophysiology

Globally about 5-15% of women and in the Indian subcontinent, 3.7-22.5 % of women of reproductive age are suffering from PCOS (Ganie et al., 2019). As shown in figure 1, in PCOS the gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and progesterone is decreased whereas luteinizing hormone (LH), prolactin, antimullerian hormone (AMH), androgens and estradiol are significantly increased. The pulsatile release of GnRH is imperative for fair levels of FSH and LH homeostasis. However, in PCOS the variant pulsatile release of GnRH leads to an increased LH/FSH ratio and causes excessive prolactin (PRL) leading to a decrease in GnRH secretion. Low concentration of FSH and progesterone adds stress to a regulatory feedback loop of the hypothalamus leading to increased abnormal pulsatile secretion of GnRH (Patel, 2018). A basal level of AMH secreted from granulosa cells is required for follicle development. The increased AMH in granulosa cells in PCOS neutralizes the FSH role and interferes with early folliculogenesis affecting ovulation. LH-induced surge is necessary for COX-2(cyclooxygenase 2) gene expression and PEG2 (prostaglandin E2 receptor) actions in cumulus-oocyte complex required for mediating a large number of biochemical changes in granulosa cells of mature follicle, which promotes transformation in proliferating cells, degradation of extracellular matrix in follicle wall and delineation events responsible for ovulation. However, in PCOS such LH surge is unseen instead continued increase of LH occurs throughout the cycle leading to anovulation or oligoovulation. The swollen fluid-filled graffian follicles arrested in the ovulatory phase without ovulation are cysts. Accumulation of such cysts leads to polycystic ovaries and in absence of ovulation the postovulatory function of granulosa cells to synthesize progesterone aborts leading to improper development of endometrium and implantation defeat (Ganie et al., 2019). Accumulations of cysts create an inflammatory response and increase anti-inflammatory biomolecules such as interleukins and cytokines thought to play role in the pathogenesis of PCOS. The serum prolidase activity and androgen level from the adrenal cortex are also elevated in PCOS directly affecting the extracellular matrix of the ovary and interfering with the signaling, responsible for the proliferation and differentiation of follicles (Bhatnager et al., 2018). The principal pathophysiology responsible for PCOS is multifactorial and likely heterogeneous among affected individuals. Multiple aspects of the hypothalamic-pituitary-ovarian (HPO) axis are dysfunctional. Intrinsic ovarian differences in steroidogenesis, neuroendocrine dysfunction, insulin resistance/hyperinsulinemia, nutrient excess, ectopic fat storage, inflammatory factors, genetic influences, and epigenetic changes interact with environmental exposure to culminate into PCOS.

Leptin, adiponectin and oxidative stress

Leptin is a major intermediary between nutritional status and the reproductive health of women. A high level of leptin has been associated with the markers of insulin resistance (IR) in PCOS patients. PCOS patients had higher leptin levels as compared to controls, and leptin levels also were positively correlated with serum testosterone levels. Case-control studies demonstrated lower serum adiponectin levels in women with PCOS as compared to controls. The adiponectin levels were lowest in obese women with PCOS and even non-obese PCOS patients had low adiponectin which improved with metformin treatment. The role of adiponectin in PCOS pathogenesis in animal studies shows that adiponectin treatment reduces androgen synthesis in DHEA-treated PCOS mice in an in vitro study (Singh et al., 2017). The plasma leptin-adiponectin ratio is positively associated with markers of metabolic syndrome and IR, the lower

adiponectin levels being a potential biomarker of metabolic risk and IR in PCOS patients.

Emerging information shows that increased Oxidative Stress (OS) and decreased antioxidant status are also linked with PCOS. Plasma amino acid levels are significantly deranged in PCOS patients suggesting a marker of higher metabolic and oxidative stress. Past studied stated the genomic instability and cytotoxicity due to oxidative stress by estimating the frequency of micronucleated cells in epithelial samples and serum malondialdehyde levels respectively, and found a positive correlation in patients with PCOS suggesting high oxidative stress in PCOS patients. Researchers investigated the markers of oxidative stress and high-sensitivity C-reactive protein levels in patients with PCOS and found that both are significantly elevated. Reduced arginine bioavailability found in PCOS patients is correlated with low nitric oxide levels and increased oxidative stress. Thus, reactive oxygen species induce OS in PCOS patients. Lately, the experts have determined the role of xenopsin (an octapeptide) in polycystic ovarian syndrome and have shown a significant increase in Xenopsin levels in PCOS patients.

Genetic and molecular causes

The consequence of PCOS manifests throughout a woman's lifespan. Studies have effectively proven the associations of genes and their SNP's associated with the pathogenesis of PCOS. The study of genes involved in regulating ovarian functions, adrenal gland cells, lipid metabolism, insulin resistance, and hyperandrogenism can increase the understanding at the molecular and genetic levels. Surprisingly every population shows variation in SNPs of a particular gene involved in pathogenesis. In a combined effect, some genes may be specific to a particular population and some may be common. Molecular analysis of several genes helps in creating a molecular signature of genes as a diagnostic approach to detect PCOS. Many candidate genes have been identified to be one of the causes of PCOS. Different studies have been carried out to find the genetic correlation of PCOS. Ajmal et al. (2019) reviewed a study that identifies the clear cause of PCOS and its genetic association and hormonal disbalance. The genes involved in pathogenesis are reported and presented in *Table 1*. Alteration in expressions of genes CYP17, CYP21, CYP11a, and CYP19 are involved in steroidogenesis in granulosa cells and adrenal gland cells leading to increased levels of androgens. The alterations in gene expression are also due to insulin resistance in granulosa cells and proven that due to a deficiency of vitamin D, insulin resistance increases in the body (Siddamalla et al., 2018). Aberrant DNA methylation is also an important contributing factor to PCOS pathological changes. DNA methylation level in granulosa cells is reduced in PCOS (Cao et al., 2021).

Table 1. *The reported genes involved in the pathogenesis of PCOS. Summary of genes identified, SNP location, chromosome location, and pathogenesis.*

Sr no.	Gene name	SNP location	Chromosome location	Pathological conditions and population showing occurrence	Source
1	FSHR	p. Thr307Ala or p. Asn680Ser	2	Impaired folliculogenesis in the Korean population	Kim et al. (2017)
2	LHCGR	rs13405728	2	Oligo or Anovulation in Han Chinese women	Cui et al. (2013)
		rs61996318	2	High LH/FSH ratio, Insulin resistance, oligomenorrhea, Polycystic morphology in the Indian Population	Deswal et al. (2019)

		rs2293275 &	2	BMI, LH/FSH ratio and Insulin resistance in South Indian	Thathapudi et al. (2015)
3	LHβ	rs1056917	19	High LH/FSH ratio, Insulin resistance, oligomenorrhea, and Polycystic morphology in the Indian population	Deswal et al. (2019)
4	KISS1	rs4889	1	Increased LH levels in Saudi Population	Albalawi et al. (2018)
5	DENND1A	rs346803513	9	Associated with the increased risk of PCOS Chinese population	Chen et al. (2017)
		rs2479106	9	Insulin resistance and Polycystic ovarian morphology in the Han Chinese population	Cui et al. (2013)
6	THADA	rs13429458	2	Increased levels of Testosterone and LH in the Han Chinese population	Cui et al. (2013)
		rs12478601	2	Elevated LDL concentrations and dyslipidemia in Han Chinese women	Cui et al. (2013)
7	IRS 1	Gly972Arg	2	Associated with increased susceptibility of PCOS in the Caucasian Population	Shi et al. (2016)
8	IRS 2	Gly1057Asp	13	Associated with increased susceptibility to Asian ethnicity	Shi et al. (2016)
9	VDR	Bsm I A/G, Apa I A/C, Taq I T/C	12	Constitute as an inheritable risk factor of PCOS in the South Indian population	Siddamalla et al. (2018)
10	IL-6	rs1800795	7	High BMI, insulin resistance, hirsutism, high testosterone, and oligomenorrhea in Indian, Turkey, German, Spain, and Austria population	de Alencar et al. (2016)
11	IL-17A	rs2275913	6	No association with either pathological condition in the Iranian population	Hesampour et al. (2019)
12	RAB 5B	rs1045435, rs11550558, rs705700, rs11171718	12	Increase of LH and testosterone levels in Han Chinese	Yu et al. (2019)
13	CAPN10		2	Insulin resistance in PCOS subjects	Ajmal et al. (2019)
14	FTO	rs8050136 rs1588413	16	Oligo-ovulation with increased implantation rate in Chinese women	Liu et al. (2018)
		rs9939609	16	Obesity in the Chinese population	Cai et al. (2014)
15	MTHFR	C677T	1	Decreased activity of folate pathway observed in Italian, Egyptian, Turkish, Indian, and Polish women	Chen and Fang (2018)
16	PEPD	rs267606943	19	Increased plasma prolidase levels, anovulation in the Indian population	Bhatnager et al. (2018)
17	ADIPOQ	rs1501299	3	Influence's occurrence of Polycystic ovary morphology and altered lipid profiles in Polish Women	Czeczuga-Semeniuk et al. (2018)
18	PCSK9	rs562556 GG	1	Higher HDL-c in Brazilian PCOS females	Xavier et al. (2018)
		rs562556 AA	1	Higher plasma testosterone levels in Brazilian PCOS females	Xavier et al. (2018)
19	ND1	3155 G to A 3163 G to C 3182 T to C 3188 C to G 3285 T to C	Mitochondria DNA	Insulin resistance and anovulation in South Indian females	Inthu et al. (2020)
20	PTEN	rs1903858 A/G, rs185262832G/A and rs10490920T/C	10	The PTEN gene polymorphisms may constitute an inheritable risk factor for PCOS in South Indian women	Siddamalla et al. (2020)
21	TUBB8	-	10	Compromised oocyte developmental competence in ovarian cells of PCOS patients	Li et al. (2021)
22	TUBA1C	-	12	Compromised oocyte developmental competence in	Li et al. (2021)

				ovarian cells of PCOS patients	
23	ERV1	-	2,3,4, and 5	Compromised oocyte developmental competence in ovarian cells of PCOS patients	Li et al. (2021)
24	BMP4	-	14	Gene associated with DNA hypomethylation and miRNA co-regulated network in PCOS	Cao et al. (2021)
25	ETS1	-	11	Gene associated with DNA hypomethylation and miRNA co-regulated network in PCOS	Cao et al. (2021)
26	CYP1B1	-	2	Gene associated with DNA hypomethylation and miRNA co-regulated network in PCOS	Cao et al. (2021)
27	CYP11A1	rs4077582	15	Hyperandrogenism observed in Egyptian population	Heidarzadehpilehrood et al. (2022)
		(TTTTA)n	15	Hyperandrogenism observed in Greece and Indian population	Heidarzadehpilehrood et al. (2022)
		(AAAAT)n	15	PCOS and hyperandrogenism in the Iraq population	Heidarzadehpilehrood et al. (2022)
28	CYP17A1	rs743572	10	PCOS symptoms in Chile, Indian, Iran, Iraq, and Pakistan population	Heidarzadehpilehrood et al. (2022)
29	CYP19A1	(TTTA)7	15	Ovulatory dysfunction in Greece and China	Heidarzadehpilehrood et al. (2022)
		rs2470152	15	Polycystic ovarian morphology in the Chinese and Indian population	Heidarzadehpilehrood et al. (2022)
		rs2414096	15	Oligomenorrhea in Iran, Egypt, and Iraq	Heidarzadehpilehrood et al. (2022)

Studies found that DNA hypomethylation regulates key genes associated with PCOS and that several of the differentially methylated genes are also altered in blood samples from women with PCOS compared with healthy controls. The transmission of PCOS traits to future generations occurs via an altered landscape of DNA methylation and they propose methylome markers as a possible diagnostic landmark for the condition, while also identifying potential candidates for epigenetic-based therapy. Investigations also demonstrate that genes involved in microtubule processes, TUBB8 and TUBA1C, are overexpressed in PCOS oocytes. The metabolic and oxidative phosphorylation pathways are also dysregulated in both oocytes and cumulus cells from PCOS patients. Moreover, in oocytes, differentially expressed transposable elements are not uniformly dispersed in human chromosomes. Endogenous retrovirus 1 (ERV1) elements located on chromosomes 2, 3, 4, and 5 are rather highly upregulated (Li et al., 2021). The aberrantly elevated expression of TUBB8 and TUBA1C and ERV1 provides additional markers for PCOS and may contribute to the compromised oocyte developmental competence in PCOS patients (Li et al., 2021). These findings have implications for treatment strategies to improve oocyte maturation and pregnancy outcomes for women with PCOS.

Environmental factors

Epigenetic modifications may contribute to transgenerational inheritance where three generations may be simultaneously exposed to an unfavorable metabolic environment- the patient, her fetus, and the germ cells of the fetus. Rather than being mediated by classical genetic changes, the "messaging" can be mediated by epigenetic modifications. Environmental factors directly affect the extent of expression, methylation pattern, and mutations of genes. In PCOS environmental factors have a colossal contribution to its etiology. The air we breathe, the water we drink, crops, and vegetables are all tainted with pollutant chemicals and preservatives which act as a potent environmental influencers on gene regulation of endocrine glands. The persistent organic pollutants (POP), phthalates, bisphenol A, parabens, and benzophenone-3 act as

endocrine disruptors (EDC) and contribute to endocrine disorders. Bisphenol A is considered to be an estrogenic compound. In animal models, parabens have proved to have estrogenic and anti-androgenic properties (Kolatorova et al., 2018). Bisphenol A, chlorophenols, benzophenones, and parabens are associated with changes in ovarian and pituitary hormone levels. EDCs cause endocrine disturbances by interacting with nuclear receptors such as α, β Estrogen receptors, androgen receptors. These endocrine-disrupting chemicals alter the estrogenicity of the tissues expressing the estrogen receptors.

Exposure to these environmental stressors during fetal growth and pubertal stage leads to low birth weight, the decline in the age of puberty onset, attention deficit disorder (ADHD), autism spectrum disorder (ASD), congenital hypothyroidism, and obesity (Grimaldi et al., 2015). These chemicals even pass through the placenta and breast milk to the infant. Phthalate metabolites and high molecular weight phthalates show an association with an increased deviation of allele-specific expression of the H19 non-coding gene having a role in embryonic and placental growth. However, neither methylation nor impaired expression showed a significant impact on birth weight and length. Environmental phenols show an effect on pubertal development in girls for example the urinary concentration of 2,5 dichlorophenol is associated with early menarche and associated with increased risk of breast cancer (Wolff et al., 2015). Phenols and parabens are associated with lower TSH and T4 levels in pregnant women. The endocrine-disrupting molecules also act as obesogens indulged in the pathogenesis of obesity. Lifestyle change has enhanced the effect of environmental pollutants and chemicals on hormonal imbalance. Increased use of cosmetics mainly sunscreens rich in Benzhophenone-3, use of plastics rich in bisphenol A, increased use of room deodorizers rich in 1,4 dichlorobenzene which metabolizes in 2,5 dichlorobenphenol are key factors contributing for increased contact of individuals with metabolic disruptors.

Metabolic factors

With an upsurging rate of excessive weight gain in PCOS, lifestyle intervention is still equally effective in women with or without PCOS. Obesity is a global epidemic that deteriorates the quality of life and triggers various metabolic disorders. Obesity shows a relation to acute chronic inflammation and insulin resistance, which are potent parameters in PCOS. Obesity-induced low-grade inflammation in the hypothalamus and peripheral tissues results in whole-body insulin resistance in all the tissues. It is reported that Resistin/TLR4 signaling pathway plays a role in the onset of hypothalamic inflammation and insulin resistance (Benomar and Taouis, 2019). Increased insulin resistance due to low-grade hypothalamic inflammation creates a rise in the intensity of metabolic syndrome, which alters the steroidogenesis in gonads and adrenal glands. An imbalance in levels of sex hormones created due to metabolic syndrome affects reproductive physiology. Oxidative stress also significantly increases metabolic syndrome further increasing insulin resistance, dyslipidemia, and β cell dysfunction making them prone to type two diabetes mellitus. Insulin resistance makes weight loss a challenge creating a vicious circle of interdependent metabolic anomalies, which affect endocrine, reproductive, and other physiology. The impact of environmental influences such as food availability, activity, shared family lifestyles, and stress cannot be excluded. Thus, the genesis of PCOS is a result of various anomalies as depicted in *Figure 2*.

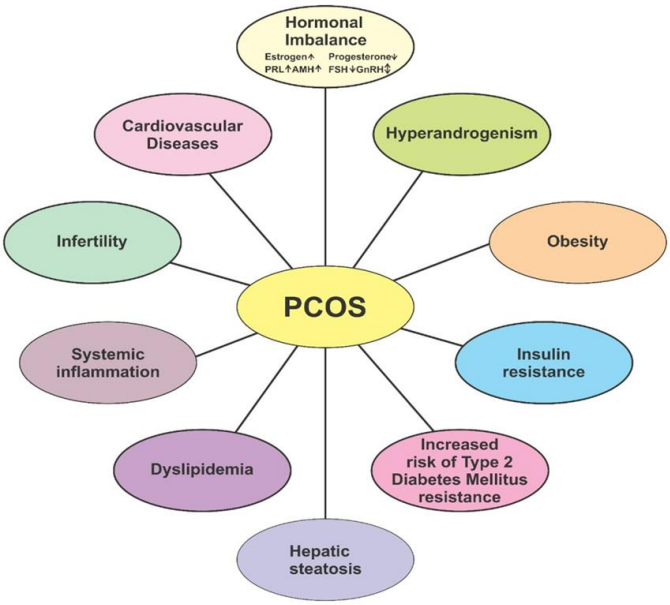

Figure 2. *A cluster of anomalies is associated with PCOS. PCOS is a result of various anomalies leading to infertility and systemic inflammation.*

Circadian rhythm

Patients with PCOS are found with significantly higher melatonin levels in the morning and smaller mean night-day differences in the concentrations of melatonin in comparison with those with non-PCOS. Circadian rhythm has a direct effect on levels of cortisol hormone in the body during PCOS (Lim et al., 2019). Augmented levels of cortisol indicate stress, showing the effect on the hypothalamus affecting the circulating sex hormones showing the effect on the pineal gland. Increased testosterone level increases serum melatonin and cortisol, used as a biomarker for identifying PCOS (Lim et al., 2019). Melatonin affects various systems contributing to PCOS pathogenesis. In PCOS, the serum melatonin level increases during the daytime followed by an increase in cortisol levels disrupting the rhythm of the day-night cycle. These differences in levels of melatonin have been associated with insulin resistance along with obesity. Lack of sleep further increases oxidative stress and cortisol-induced stress. In PCOS, the level of melatonin in preovulatory follicles decreases affecting their responsiveness to gonadotropins.

The increased levels of melatonin in follicles are essential for their proper development and secretion of progesterone hormone along with the maintenance of normal LH and FSH levels. Accordingly, in PCOS lower levels of progesterone are observed. Melatonin is also essential in maintaining the apt action of reductase and calatase enzymes. The decreased tissue levels of melatonin lead to an increase in oxidative stress in ovarian cells affecting sex hormone secretion. Increased testosterone levels affect the expression of circadian rhythm genes such as PER2 in human granulosa cells. Circadian rhythm genes show an association with steroidogenesis in ovarian cells. Differences in melatonin levels lead to increased oxidative stress leading to increased insulin resistance in ovarian cells as well as other tissues. Circadian rhythm also affects steroidogenesis leading to increased obesity in PCOS females. There is a significant correlation between night shift work and PCOS. PCOS-model rats present distinct differences in the circadian variation of corticotropin-releasing hormone,

adrenocorticotropic hormone, prolactin, and a 4-h phase delay in thyrotropic hormone levels. A significant association is established between night shift work with PCOS, and genome-wide chronodisruption exists in ovarian granulosa cells. The changes in melatonin in women with PCOS could help in elucidating the complex pathophysiological pattern of the disease.

Drugs and nondrug prophylaxis to relieve PCOS

The reproductive hormone balance can be restored using medications. To date best therapy for PCOS is to administer female sex hormones externally using contraceptive pills. Androgen-reducing drugs such as spironolactone and finasteride are used to reduce hyperandrogenism. Spironolactone can reduce androgen-induced acne and finasteride is used to reduce androgen-induced hair loss along with hirsutism (Patel, 2018). Insulin resistance is decreased using the intake of Magnesium, Zinc, and chromium supplements. Metformin helps in reducing glucose tolerance. Inositol is effective in reversing the PCOS etiology in nine out of ten patients. Vitamin D supplementation shows significant improvement in insulin sensitivity and decreases androgen levels. Right medication changes in lifestyle, and limited exposure to hormone-altering xenobiotics and odorant compounds have shown to be effective methods to decline PCOS. Since the administration of drugs can decline the severity of PCOS but there is no assurance of cure. Since various parameters are interdependent for the pathogenesis of PCOS one must increase its understanding of each of them. The causative factors mentioned so far show alteration according to populations in their severity. Therefore, more studies are a must for a better understanding of treatment and management.

Overseeing PCOS will be liable for paying a high price not only by compromising fertility during reproductive age but also developing many enduring impediments for a lifetime. Traditionally the treatment of patients with PCOS has focused on the relief of symptoms. Awareness about PCOS and its causative factors can prevent it from becoming a global epidemic like obesity. Early identification of girls “at risk” for PCOS; and together with the condition should be a priority. Weight loss has been associated with improved ovulation and pregnancy rates in women with PCOS. A regular exercise program coupled with a balanced healthy diet is the word campaigned for PCOS as nondrug prophylaxis. Lifestyle intervention guidelines recommend patients with PCOS adopt healthy lifestyles for themselves and promote healthy lifestyles for their extended families to ensure the realization of healthy habits from early childhood for their children. The Evidence-Based Guidelines have clarified the diagnostic criteria and refined the diagnosis of PCOS in adolescent girls. Patients with PCOS serve as probands or “early warning alerts” for their extended family members. Yoga practices like Asanas, Ujjayi, Pranayama, Bhrasrika Pranayama, and Shatkarma have been proven to be very beneficial in the management of PCOS as they help in eliminating the root causes like lack of physical activity, stress, and less self-control (Verma and Kaur, 2022).

PCOS is an indelible disorder with a high cost of physiological anomalies and infertility. The disease dates back 60,000 years but the severity and range of etiological factors have changed over the years (Bhalerao and Aranha, 2021). The change in the lifestyle and working pattern of females causes increased stress leading to metabolic anomalies in sex hormones. The available literature increases our knowledge in this regard to the causative factors of PCOS and it states that alteration in gene expressions,

changes in gut microbiota, development of metabolic syndrome, insulin resistance, dyslipidemia, acute inflammation, excessive androgens, and decrease in female sex hormones are responsible for the pathogenesis of PCOS. Environmental pollutants and xenobiotic compounds directly alter the reproductive hormones as well as increase the risk for the development of metabolic disease and insulin resistance. A disturbance in circadian rhythm induces oxidative stress that further creates metabolic anomalies indicating the instigation of PCOS is due to a cluster of several anomalies.

Modification of lifestyle like healthy eating habits, getting proper sleep coupled with regular physical activity will help patients to manage as the illness is not mendable. A continued PCOS state can cause great damage and change the tendency of the body making it prone to many more metabolic disturbances leading to complications like increased cardiovascular disorders and risk of type 2 diabetes mellitus (Patel, 2018). Further, studies show that a person with type 2 diabetes mellitus is at a high risk of developing Alzheimer's. Prolonged disturbances in female sex hormones increase the risk of ovarian, breast, and endometrial cancer during reproductive as well as post-reproductive age. If PCOS remains untreated in reproductive age the high levels of testosterone affect the neurological development of the child carried by the affected female, likely to have autism. Prolonged exposure to metformin can show a negative effect on children like increased BMI and overweight at the age of four born to PCOS patients treated with metformin from the first trimester until delivery. Focused studies on PCOS will help in designing a novel therapeutic measure. Creating a molecular signature for the etiology of PCOS will help in the proper diagnosis and implementation of specific treatment ruling out the trials of various treatments on patients and reducing exposure to excessive therapeutic chemicals.

Conclusion

PCOS is an alarming endocrinopathy recognized as an important contributor to multiple medical and reproductive problems. It is not a sole disease but comprehends a cluster of them and the incidence of which are on the sharp rise disrupting fertility, affecting overall health hovering post-menopause. PCOS patients undergoing ovarian stimulation have more oocytes; however, the poor quality of oocytes leads to lower fertilization and implantation rates, decreased pregnancy rates, and increased miscarriage rates. The complex molecular mechanisms underlying PCOS and the poor quality of oocytes remain to be elucidated. Although the real consequence of PCOS on life expectancy is not established, it is very apparent that the quality of life depreciates due to drug dependency. Diagnostic criteria are still evolving although currently, the Rotterdam criteria remain the most widely accepted. Future investigations must concentrate on early diagnosis, understating the genetics and molecular mechanism of the advent of PCOS. As of now, the only way out advocated is to have a better lifestyle through a healthy diet and regular exercise.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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