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POLYCYSTIC OVARIAN SYNDROME AND ITS METABOLIC CONSEQUENCES: A MINI REVIEW

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ABSTRACT: Polycystic ovarian syndrome (PCOS) is a reproductive metabolic disorder affecting nearly 20% females, globally. Though Rotterdam consensus is widely used for assessment, it lacks definite diagnostic guidelines. Absence of PCOS guidelines for adolescent and post-menopausal women might be influencing the prevalence data. The prevalence varied with ethnicities and found high in urban than rural. Among women in reproductive age, the obese rural population also found vulnerable to PCOS, indicates the role of lifestyle factors in this syndrome. Erratic lifestyle predisposes to insulin resistance, or obesity leads to subsequent hyperinsulinemia and hyperandrogenemia. Also, genetic predisposition to hypothalamic pituitary gonadal (HPG) axis dysfunction and impaired ovarian steroidogenesis further influence the disorder. It dysregulates the oocyte maturation leading to polycystic ovaries, thereby, affects the normal ovarian functions. The environmental toxins which are endocrine disruptors further worsens the consequence of the disorder. Multiple factors make it difficult to decipher the independent pathway of pathogenesis. Apart from ovulatory and reproductive dysfunctions, PCOS have chronic metabolic consequences: cardiovascular disease (CVD), obesity, dyslipidemia, obstructive sleep apnoea, and non-fatty liver. These factors are interdependent and progressive. Since the studies have contradicting results; it's difficult to determine the impact of these consequences. Both non-obese and obese PCOS women found vulnerable to the same metabolic consequences. Hence, further long term, controlled studies are required to understand the exact pathogenesis and metabolic consequences both in obese and non-obese PCOS women. Moreover, both regional and multicentre cohort studies are required to understand the progression of disease in different ethnicities.

INTRODUCTION: Polycystic ovarian syndrome, (PCOS) earlier known as the Stein Leventhal syndrome, is a multisystem endocrine disorder with reproductive and metabolic consequences [1]. The characteristic clinical features range from hirsutism, androgenic alopecia [2], acne, insulin resistance [3], acanthosis nigricansin [4], to menstrual dysfunction [5].

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Also, PCOS accounts for overweight, obesity, and anovulatory infertility [6]. The anxiety of infertility is high among these patients and might influence their quality of life [7]. Though numerous studies are being done in line with the etiology of PCOS, still the mechanism of pathogenesis and its metabolic impact remains variable and inconclusive. In that regard, this review tries to summarize the existing mechanistic evidence and metabolic consequences of PCOS and the possible avenues for future research.

Prevalence of PCOS: Azziz *et al*., report a 6.6% prevalence of PCOS in females aged between 18-45yrs [8]. Similarly, a meta-analysis in 2015 revealed a prevalence ranging from 6.8%-19.5% across the

globe [9]. Another meta-analysis reports the prevalence of 5.6% in Chinese women, contrary to 16% among the women in the Middle East. Genetics, lifestyle factors environment, and ethnicities influence both the incidence and pathogenesis of PCOS [10, 11]. Urban women have a high risk of PCOS compared to rural women [12,] but among the rural population, obese participants account for the higher prevalence of PCOS [5]. A higher proportion of adolescent school going girls from upper socio-economic status also suffers from PCOS [13]. Poor lifestyle, irrespective of the region modulates the incidence of PCOS. These suggest the impact of lifestyle factors in this disease.

Even though epidemiological studies use different diagnostic guidelines for PCOS, Rotterdam consensus 2003 criteria are widely used. However, it is difficult to determine the exact prevalence because of the lack of gold standard diagnosis guideline [7]. The National Institute of Health (NIH) 2013, an update of the Rotterdam consensus 2003, provides clarity in diagnosis by classifying PCOS into 4 phenotypes: A & B(Classical), C & D, (see **Table 1**) [14]. Nonetheless, the prevalence from most studies represent data from individuals visiting clinics rather than the general population and didn't estimate the phenotypic distribution of PCOS. Moreover, lack of awareness and social stigmas might also influence the prevalence data, especially in developing countries.

Acne affects 20%-40% of PCOS women [15]. Hirsutism is present in 60% of PCOS patients; however, only 5% have androgenic alopecia [16]. Obesity affects 30%-75% of PCOS patients. Most of them have an android body-fat distribution with a disproportionate amount of visceral body fat [17]. Polycystic Ovary (PCO) is not only present in 75% of PCOS patients but also in 20% of healthy women. The majority of PCOS patients have both functional ovarian and adrenal hyperandrogenism [18]. The high androgen levels are evident in 60% to 80% of PCOS patients and dehydroepiandrosterone (DHEA) is high in more than half of these patients [19]. Approximately 75% of PCOS females express characteristic anovulatory symptoms [20].

TABLE 1: DIAGNOSTIC CRITERIA FOR PCOS

NIH 1990 [21]	ROTTERDAM 2003 [16]	AE PCOS 2006 [22]	NIH 2012 [23]
Both criteria should be met. a. Clinical and biochemical signs of hyperandrogenism. b. Chronic anovulation.	Two of the three conditions should be present. a. Oligo and/or anovulation. b. Clinical or biochemical hyperandrogenism. c. Polycystic Ovaries.	Both criteria should be met. a. Clinical and/or biochemical signs of hyperandrogenism. b. Oligo and/or anovulation or Polycystic Ovaries.	Two of the three conditions should be present and identify the specific phenotypes. a. Clinical and/or biochemical signs of hyperandrogenism. b. Oligo and/or anovulation. c. Polycystic Ovaries.

In all the criteria, the other aetiologies for Ovulatory dysfunctions and Hyperandrogenism should be excluded. e.g., Adrenal Hyperplasia. NIH –National Institute of Health. AE-PCOS – Androgen Excess & PCOS society. Specific Phenotypes include (A) Hyperandrogenism & Oligo and/or anovulation, (B) Hyperandrogenism & Polycystic Ovaries (C) Oligo and/or anovulation & Polycystic Ovaries (D) Hyperandrogenism, Oligo and/or anovulation & Polycystic Ovaries [24]

Aetiopathogenesis of PCOS:

Hypothalamic Dysfunction: The pathogenic mechanisms of PCOS are debatable. The hypothalamus releases gonadotropin-releasing hormone (GnRH) that modulate the anterior pituitary to release both luteinizing hormone (LH) and follicular stimulating hormone (FSH). The hypothalamic pituitary gonadal axis (HPG Axis), regulates the secretion of steroid hormones [24]. Kisspeptin -neurokinin-β -dynorphin (KNDy) neuronal network determines pulsatile GnRH secretion [25]. Umayal et al observed PCOS women have higher serum kisspeptin levels than normal women [26]. Additionally, studies associate PCOS to neuroendocrine impairment and dysregulated kisspeptin pathway [27, 28]. In PCOS pulsatile GnRH favours hypersecretion of LH which consequently causes hyperandrogenaemia. PCOS women respond to an acute GnRH-agonist challenge test [29]. An imbalance in LH/FSH ratio impairs oocyte maturation causing anovulation [30]. However, studies suggest LH stimulation lacks influence in ovarian hyper androgen secretion [31]. It sheds light on an intrinsic ovarian abnormality for hyperandrogenism in PCOS.

Role of Insulin: A defect in the post binding signaling pathway causes insulin resistance in

PCOS. However, the number of receptors and binding capacity of insulin is not compromised in PCOS. Protein kinase C mediates excessive serine phosphorylation of insulin substrate receptor (IRS1) and results in insulin resistance. Free fatty acid (FFA) accumulation also mediates serine phosphorylation [3, 29, 32].

Compensatory hyperinsulinemia is associated with the pathogenesis of PCOS. A systematic review by Behboudi- Gandevani *et al*., revealed a higher incidence of insulin resistance (pooled mean- 4.38, 95% CI: 3.84-4.92) in obese-PCOS than non-obese-PCOS and control women [33]. Insulin regulates sex hormone binding globulin (SHBG) synthesis. SHBG regulates the free steroidal hormone levels in the blood by transporting it to intracellular target locations [34]. Suppression of insulin secretion with diazoxide increases SHBG [35]. Reduced SHBG levels elevate free testosterone, further reduces SHBG production. This causes hyperandrogenism. A metanalysis by Deswal *et al*., demonstrates a reduction in SHBG levels in PCOS patients, irrespective of obesity (SMD; -0.83, 95% Ci:- 1.01, -0.64) [36]. Insulin resistant PCOS women have a lower concentration of SHBG than noninsulin resistant PCOS. Moreover, high Free testosterone levels are seen in insulin-resistant PCOS group (p=0.005) [37].

Thecal cell culture secretes excess androgen in response to insulin and LH compared to non-PCOS thecal cell culture. Overexpression of steroidogenic enzyme CYP17 is seen in non-PCOS cells [38]. It suggests an independent intrinsic effect of insulin in ovarian steroidogenesis, independent of obesity and T2DM, in PCOS women. Though proper etiology is unclear, insulin seems to have both independent and mediating roles in the pathogenesis of PCOS.

Role of 5α- Reductase: 5α-reductase reduces testosterone to dihydrotestosterone, which binds to the androgen receptor to form an androgen-receptor -dihydrotestosterone complex. This complex has a longer half-life and is more potent than androgen-receptor-testosterone complex[39]. High 5α-reductase levels associate with insulin resistance independent of obesity [40]. A meta-analysis by Wu *et al.* demonstrates higher proportions of 5α-reductase metabolites in PCOS women compared to BMI matched controls. Moreover, subgroup analyses confirm the association of 5 α reductase with insulin resistance [41]. 5α-reductase indirectly modulates hyperandrogenism; however, the exact mechanism is unclear.

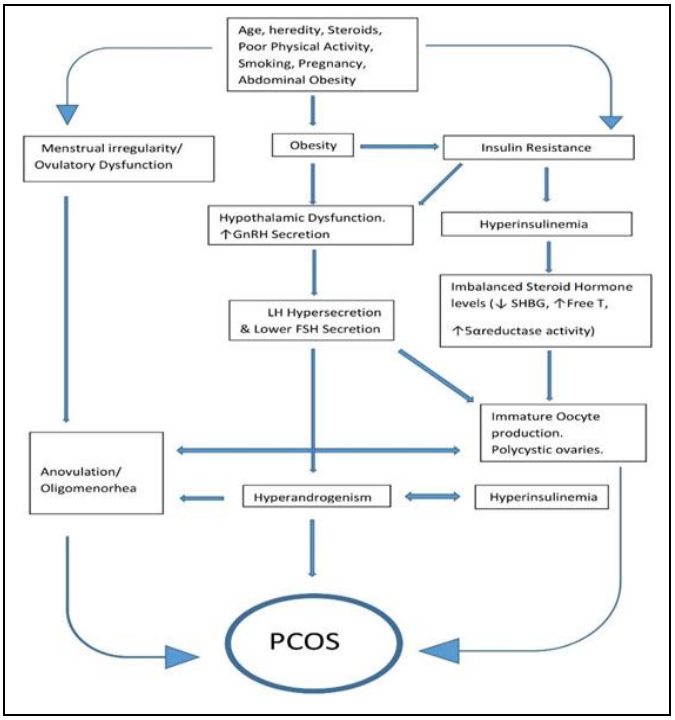

FIG. 1: A SCHEMATIC REPRESENTATION OF AETIOPATHOGENESIS OF POLYCYSTIC OVARIAN SYNDROME

Environmental Toxins: Endocrine disrupting chemicals (EDC) from the environment interferes with the hormone system. The serum concentration of bisphenol A (BPA) is elevated in PCOS women [42] and strongly associated with androgens [43]. Elevated BPA levels can also be found in adolescent girls with PCOS [44]. BPA is present in polycarbonate plastics and it migrates to packed foods [45]. Animal studies reveal neonatal exposure of BPA alters HPA axis and associated with the development of PCOS [46]. In rat ovarian interstitial thecal cells, BPA induction modulates the enzymes responsible for ovarian steroidogenesis [47]. BPA competitively binds with SHBG and displaces androgens leading to increased free testosterone levels [48].

Moreover, BPA downregulates CYP2C11 and CYP3A2 enzymes that metabolize androgens [49]. These androgens inhibit uridine glucuronosyl-transferase (UGT) that metabolize BPA [50] and consequently leads to prolonged higher circulating

BPA levels. A recent study reveals BPA metabolite 4-Methyl-2, 4-bis (4-hydroxyphenyl) pent-1-ene (MBP) binds with endogenous androgen and progesterone receptors and causes target tissue dysfunction [51]. However, most of the EDC studies have employed animal models to explain the etiopathogenesis of BPA in PCOS. More longitudinal epidemiological studies are required to explore the role of different EDCs in PCOS.

Metabolic Consequences: Compensatory hyper-insulinemia due to insulin resistance results in metabolic abnormalities like hypertension, obesity, dyslipidaemia, cardiovascular disease, and obstructive sleep apnoea [52].

Dyslipidaemia: PCOS women have elevated: serum insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA IR), and lipid levels [53]. Dyslipidaemia affects more than two-thirds of PCOS women[54]. High concentration of low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides, and low high-density lipoprotein cholesterol (HDL-C) is evident in PCOS women [55]. On the contrary, PCOS women had similar lipid levels as the controls except for HDL-C and apolipoprotein A (Apo A) [56]. Also, PCOS is associated with elevated triglycerides (OR -1.48 [95% CI, 1.08-2.03]), a major risk factor for cardiovascular diseases [57].

In PCOS, both the quantity and quality of lipid changes. PCOS women have low HDL_2, the anti-atherogenic HDL subtype, and high atherogenic small dense LDL-C. Both are independent predictors of cardiovascular morbidity and mortality [58]. A meta-analysis in 2011 reveals, 26mg/dL (95% confidence interval [CI] 17-35) and 12mg/dL (95% CI 10-16) increase in triglyceride and LDL-C levels in PCOS women than normal women along with 6 mg/dL (95% CI 4-9) decrease in HDL-C [59]. However, a recent meta-analysis by Amiri *et al.* contradicts that, no significant associations of testosterone with metabolic parameters of PCOS. However, after adjusting for age and BMI they found an association, but only with LDL (β = 0.006; 95 % CI: 0.002, 0.01) and HDL (β = –0.009; 95 % CI: –0.02, –0.001) [60]. It suggests the independent influence of age and BMI in determining the metabolic consequences of PCOS and its importance in the course of cardiovascular diseases. Though the exact mechanism of dyslipidemia in PCOS remains clouded, studies suggest that obesity, hyperinsulinemia, and hyperandrogenaemia mediate its pathogenesis [61].

Obesity: Obesity affects the development and the progression of PCOS by influencing the severity of its associated metabolic disturbances. Android obesity is a specific risk factor for PCOS [62]. Fat deposition in the abdominal wall and visceral mesenteric locations cause android obesity in an ovulating overweight women with excess androgens [63]. Androgenic obesity, in turn, causes insulin resistance, glucose intolerance, diabetes mellitus, and high androgen production.

Moreover, high fat to lean mass (F/L ratio) is independently associated with insulin resistance in PCOS women [64]. A 40% decrease in GLUT 4 transporters indicates a post-signaling defect in insulin receptors. However, the affinity of the receptors remains unchanged [3, 65]. Hyperandrogenism causes metabolic dysfunction through deposition of fat in the intra and subcutaneous - abdominal adipocytes [66]. Hyperandrogenaemia, insulin resistance, and central obesity independently and interrelatedly influence the etiology of PCOS. A 12-week exercise intervention that reduces central obesity -0.40 (-0.60, -0.21); (P=0.01), improves insulin sensitivity [67]. This combination of insulin resistance, excess androgen, and central obesity is a specific feature of PCOS. Central fat deposition increases low-grade inflammation and insulin resistance, independent of age and BMI [68].

Hemostatic parameters, especially coagulation factors, strongly correlate with central fat in PCOS women [69]. It suggests an intrinsic CVD risk mediated by adipose tissue of PCOS women. The etiology of obesity and PCOS seems to be bidirectional. For instance, a 5% loss of weight in obese PCOS women, improves hyperandrogenic symptoms by 40% [70]. Lifestyle modifications might improve insulin resistance and hyperandrogenism. Weight loss can also restore menstrual regularity and fertility.

Cardiovascular Disease (CVD): PCOS increases the risk of cardiac disease [71]. CVD events [Hazard

Ratio =1.7 (95% CI, 1.7; 1.8) (P<0.001)], hypertension and dyslipidaemia are common in PCOS women [72]. A meta-analysis by Groot *et al*. identifies a relative risk of 2.02 (95% confidence interval 1.47-2.76) for Coronary heart disease (CHD) or stroke in PCOS women than healthy controls. The risk for CHD events remains high, even after adjusting for BMI [73]. Another meta-analysis on the inflammatory marker reveals 96% (95% confidence interval, 71%–122%; z¼ 7.32) increase in circulating CRP in PCOS women [74]. CRP upregulates human monocyte CCR2 expression, a monocyte chemotaxis receptor, and induces endothelial dysfunction [75].

The carotid artery intima-media thickness is increased by 0.072 mm in PCOS women [95% confidence interval (CI) 0.040, 0.105, P<0.0001] [76]. Also, the odds for carotid artery calcification (CAC) in PCOS women is 2.70 (95% confidence interval, 1.31–5.60) [77]. Women with PCOS have a larger left atrial size, higher left ventricular index, and lower left ventricular ejection fraction when compared to those without PCOS [78]. Insulin resistance, free testosterone, luteinizing hormone, and adipocytokines mediate endothelial dysfunction associated PCOS. These factors are independent risk factors for CVD. Moreover, insufficient and inconsistent data of ED in PCOS demands further research [79].

Obstructive Sleep Apnoea (OSA): Women with PCOS have a higher risk of developing OSA (hazard ratio: 2.63, 95% CI 1.57-4.04) in later life compared to their demographic-matched controls [80]. The same observation is supported in a meta-analysis by Helvaci *et al*., that exhibit a higher risk of OSA (Odds ratio =9.74, 95% CI: 2.76–34.41) in adult PCOS women [81]. PCOS women with OSA shows high plasma insulin (306.48 ± 52.39 *vs.* 176.71 ± 18.13 pmol/L, P<0.01) than controls [82]. Moreover, PCOS women with OSA have higher insulin resistant than those without OSA even after controlling for confounding factors [homeostasis model assessment (HOMA) index 5.7 ± 0.4 *vs.* 3.5 ± 0.4; P=0.006] [83]. Insulin resistance might be involved in the etiology of OSA in PCOS.

Overweight PCOS women have a higher risk of developing OSA compared to age –and weight-matched controls [84]. Waist circumference, a marker for central obesity, correlates with the severity of OSA in PCOS women [85]. The severity of obesity determines the risk of OSA in PCOS women [86]. Neck to abdominal fat percentage associates with OSA than the general obesity [87]. Fat depositions in the upper thoracic regions obstruct the airways causing OSA [88]. Further, abdominal fat accumulation reduces lung volume, increases chest wall thickness, and reduces ventilator drive [89].

Evidence from a follow-up study shows an increase in the risk of OSA in PCOS women irrespective of their obesity status (adjusted HR = 2.26, 95% CI: 1.89–2.69, P<0.001) [90]. A recent meta-analysis observes that PCOS women with OSA have metabolic abnormalities; however, the studies analyzed failed to decipher the independent effect of OSA [91]. Though obesity and insulin resistance seems to be common mechanisms linked with OSA, it requires quality research for conclusive evidence [92].

Non-Alcoholic Fatty Liver Disease (NAFLD): Nearly 40% of women with PCOS have NAFLD [93, 94]. Liver enzymes are elevated in PCOS women [95]. Metabolic abnormalities and high androgen levels in PCOS are linked to an increase in liver enzymes [96]. Insulin resistance, obesity, abdominal adiposity, and triglyceride are independent risk factors for NAFLD in PCOS women [97]. However, meta-analysis observes that PCOS with NAFLD independently associates with hyperandrogenism than any other risk factors like obesity, insulin resistance, and triglycerides [98, 99]. Kumarendran *et al.* found a similar observation where hyperandrogenism was the only independent factor that determines the course of NAFLD in PCOS women [100]. Though hyperandrogenism is associated with NAFLD in PCOS women, the influence of obesity cannot be ruled out.

Osteopontin (OPN) is a glycoprotein that involves immunity [101], inflammation, obesity, insulin sensitivity [102], female reproduction [103,] and alcoholic liver disease [104]. High OPN level associates with bioactive androgen levels and liver fat content irrespective of obesity in PCOS women [105]. OPN might predict NAFLD in PCOS.

CONCLUSION: PCOS is a major reproductive metabolic disorder found in females during

reproductive age. Its prevalence and incidence rate is increasing due to genetic, environmental factors, and improper lifestyle. Though impaired HPA axis, hyperinsulinemia, impaired ovarian steroidogenesis, and environmental toxins were hypothesized to be its pathogenesis, lack of a definite conclusion is evident. Several risk factors such as dyslipidemia, obesity, cardiovascular disease, obstructive sleep apnoea, and non-alcoholic fatty liver disease modulate metabolic abnormalities in PCOS.

The independent influence and inter-relationship of the risk factors in the course of the disease need further research. A long term longitudinal studies both in controlled and real-life settings might help in this regard. As the prevalence and its expression vary with ethnicities, regional-based assessment should be focused along with multicenter approach.

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