Review Article

The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review

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Abstract

Background: Polycystic ovary syndrome (PCOS), the major endocrinopathy among reproductive-aged women, is not yet perceived as an important health problem in the world. It affects 4%–20% of women of reproductive age worldwide. The prevalence, diagnosis, etiology, management, clinical practices, psychological issues, and prevention are some of the most confusing aspects associated with PCOS. **Aim:** The exact prevalence figures regarding PCOS are limited and unclear. The aim of this review is to summarize comprehensively the current knowledge on the prevalence of PCOS. **Materials and Methods:** Literature search was performed through PubMed, ScienceDirect, Cochrane Library, and Google Scholar (up to December 2019). All relevant articles published in English language were identified following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. **Results:** Our analysis yielded 27 surveys with a pooled mean prevalence of 21.27% using different diagnostic criteria. The proportion of women with PCOS also increased in the last decade. **Conclusion:** The current review summarizes and interprets the results of all published prevalence studies and highlights the burden of the syndrome, thereby supporting early identification and prevention of PCOS in order to reverse the persistent upward trend of prevalence.

Keywords: *Etiology, diagnostic criteria, polycystic ovary syndrome, prevalence, prevention*

Introduction

Stein and Leventhal were the first to describe polycystic ovary syndrome (PCOS) more comprehensively in 1935.[1] With varied clinical manifestations, unknown etiology, complex pathophysiology, and poor diagnosis, it has produced considerable scientific debate.[2-11] The diagnosis of PCOS remains a controversy in clinical endocrinology. In order to create an extensive and descriptive definition for the diagnosis of PCOS, the National Institutes of Health (NIH) criteria came into existence in 1990.[12] Then, in 2003, a workshop in Rotterdam formulated a new diagnostic criterion named Rotterdam criteria.[13] This criterion requires the presence of two conditions out of the three: (1) oligomenorrhea/anovulation, (2) clinical/biochemical hyperandrogenism, and (3) polycystic ovaries (≥12 follicles in each ovary measuring 2–9 mm). In 2006, the Androgen Excess Society (AES) revised the diagnostic criteria. The AES requires the specific presence of clinical/biochemical hyperandrogenism in combination with either oligoanovulation or polycystic ovaries.[12,13] The process of standardization of diagnosis confronts certain obstacles. First, in early menarche, ovulation is often irregular. Thus, anovulation cannot be considered as a definite evidence of the existence of the syndrome.[14] Second, transvaginal ultrasonography is not routinely performed in adolescents, which restricts ovary visualization and therefore excludes any invasive

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diagnosis of polycystic ovarian morphology. Third, there is a lack of consensus on the biochemical levels of hyperandrogenism, and there is limited information regarding normal levels of androgens in adolescents. Therefore, determining androgen abnormality is a complex task. Fourth, multifollicular ovaries, which may be present normally in adolescent girls, are hard to extricate from polycystic ones. Thus, the Pediatric Endocrine Society has recommended certain guidelines for differential diagnosis of PCOS in adults and adolescence. The appropriate consensus (persistent hyperandrogenic oligoanovulation) based on age and stage appropriate standards for early diagnosis and management of PCOS is summarized in Supplementary Table 1.[15]

Multiple genetic and environmental factors play an important role in occurrence of PCOS. The consequences of this multifaceted disorder extend beyond the reproductive system affecting metabolic, cardiovascular, immune, and psychological health of affected women. Over the past decade, genome-wide association studies (GWASs) have greatly advanced the understanding of PCOS pathophysiology by identifying several critical genes involved in steroidogenesis, hypothalamic–pituitary pathways, gonadotrophin action, insulin action and secretion, adipose tissue disturbances, homeostasis, lipid metabolism, and chronic inflammation are considered as the most promising genes involved in PCOS. Some of these genes are LHR, FSHR, INSR, ERB, THADA, and HMGA2.[16-20] Azziz[21] reviewed the etiology of PCOS implicating genes involved in modulation of gonadotropin and neuroendocrine action, ovarian androgen biosynthesis, and possible insulin action, providing clues to the evolutionary path and potential evolutionary advantages of PCOS. The overexpression of DENND 1A isoform produced a PCOS theca phenotype, and causal mechanisms and balancing selection were inferred from genetic associations with PCOS.[22,23] Women with PCOS have considerable varied symptomatology across life span. Physical, biochemical, and radiographic evaluations along with medical history provide confirmatory PCOS-related evidences. Hallmark features of PCOS include anovulation, hyperandrogenism, and polycystic ovaries. Other major manifestations of PCOS are as follows: Luteinizing hormone hypersecretion, metabolic disturbances, hyperinsulinemia, insulin resistance, glucose intolerance, dyslipidemia, hirsutism, acne, obesity, diabetes mellitus type II, and infertility. Various long-term complications include cardiovascular events, endometrial cancer, and psychological disorders such as stress and depression.[24-26] Table 1 represents various symptomatologies associated with the disorder. In recent years, the geographic variations of PCOS prevalence have been studied worldwide. The prevalence of PCOS is frequently quoted between 2% and 26%.[27] The differences in diagnostic criteria, sample heterogeneity, socioeconomic level, medical care access, prevalence of influential risk factors, health and education/awareness were among the possible causes of substantial geographic disparities in the prevalence rate.[28] Based on ancestral or geographical segregation, the world's populations vary in physical, social, and behavioral features due to natural selection and environmental adaptations, the conditions which then strongly influences the phenotype of the disease. It is now evident that race and ethnicity affect clinical presentation of PCOS due to different genetic and environmental predisposition to endocrine and metabolic aberrations. As reported in 2017, it was found that Hispanic PCOS women presented a higher degree of hyperandrogenism and metabolic aberrations as compared to non-Hispanic women.[29]

The need to improve the clinical and therapeutic management of PCOS patients has become increasingly evident in the last decade. Many treatment possibilities exist to correct the severity of clinical manifestations of PCOS patients. Every physician should be able to choose the most protocol in relation to PCOS and the possible prospect of a pregnancy. Table 2 includes the appropriate therapeutic techniques with pharmacological therapies in order to treat PCOS.[30-34] The key strategies for better management of PCOS included the need for specific biological markers, the use of more precise techniques for measuring circulating androgens, understanding the risk factor consequences of PCOS, and finally, treatment strategies based on individual-specific phenotype needs.

We therefore aimed to collate different prevalence studies conducted till date in order to explore key variables that may influence prevalence estimates. The present study highlighted past to present-day accepted guidelines used for PCOS diagnosis. This review also stressed on current treatment and screening guidelines used with specific emphasis on potential new therapies that can be used for better management of PCOS.

Materials and Methods

Search strategy

Two reviewers carried out a systemic computer-assisted literature search of all major databases including MEDLINE, PubMed, ScienceDirect, ISI Web of Knowledge, Embase, Google Scholar, and Wiley. The following search terms were entered as medical subject

Table 1: Clinical features associated with polycystic ovary syndrome

Clinical features	Type of clinical feature	Parameters affected
	Directly related clinical features	
Menstrual irregularities	Oligomenorrhea,	Infrequent menstruation at intervals >35 days
	Amenorrhea	Absence of menstruation
	Hypermenorrhea	Heavy and prolonged menstrual periods
Clinical hyperandrogenism	Hirsutism	Ferriman-Gallwey score ≥8
	Acne	GAGS
	Androgenic alopecia	Thinning and diffuse hair loss
	Virilization	Male pattern baldness
Biochemical hyperandrogenism	Elevated serum androgen level	Total or free serum T level
		Androstenedione,
		DHEAS
Polycystic ovaries	Numerous small cysts in a "string-of-pearls" appearance	Presence of ≥12 follicles of 2-9 mm diameter increased ovarian volume >10 ml in either ovary
AN	Papillomatosis and hyperkeratosis of skin	Scale for AN
		0: Absent
		1: Present
		2: Mild
		3: Moderate
		4: Severe
Acrochordons	Skin tags	Vary in diameter from 2 to 6 mm
	Reproductive consequences	
Infertility	Primary infertility	Failure to achieve a live birth
	Secondary infertility	
Endometrial cancer	Endometrial hyperplasia	Endometrial biopsy
	Metabolic consequences	
Metabolic syndrome	NCEP Panel III criteria	Abdominal obesity >35 inches, TG ≥150 mg/dl, HDL-C: <50 mg/dl, BP ≥130/85 mmHg, fasting glucose ≥110 mg/dl
	Any three of these symptoms	
Obesity	Defined by body mass index	BMI ≥30 kg/m^2
Type 2 diabetes (DM2)	Characterized by high blood sugar, insulin resistance, and relative lack of insulin	Fasting plasma glucose level, oral glucose tolerance test
CVD	Group of disorders of heart and blood vessels	Arrhythmia, stroke, atherosclerosis
Insulin resistance	Impaired sensitivity to insulin-mediated glucose disposal	HOMA-IR
Dyslipidemia	Abnormal amount of lipids	Elevation of plasma cholesterol, triglycerides
	Psychological features	
Anxiety	BAI	0-21: Low anxiety
		22-35: Moderate anxiety
		>36: Severe anxiety
Depression	BDI	0-9: Minimal depression
		10-18: Mild depression
		19-29: Moderate depression
		30-63: Severe depression

GAGS=Global acne grading system, T=Testosterone, NCEP=National Cholesterol Education Program, TG=Triglycerides, LDL=Low-density lipoproteins, C=Cholesterol, BP=Blood pressure, BMI=Basal metabolic rate, HOMA-IR=Homeostatic model assessment-insulin resistance, BAI=Body adiposity index, BDI=Body density index, AN=Acanthosis nigricans, CVD=Cardiovascular disease

headings for finding studies reporting the prevalence of PCOS: The search strategy used a combination of different terms "prevalence of PCOS," "epidemiology of PCOS," "PCOS in reproductive age," and "polycystic ovary syndrome." References in the identified studies were also investigated to identify additional studies. Any discrepancies regarding data extraction were resolved by mutual consensus.

Table 2: Different approaches for treatment of polycystic ovary syndrome

Category	Drug (commercial/scientific name)	Side effects
Medical therapy for irregular menstruation		
Oral contraceptive pill	Diane/Brenda/Juliet/Estelle/Yasmin/Valette	May increase insulin resistance and weight
Combined oral contraceptives	Ethinylestradiol, desogestrel, gestodene	Mood changes, bloating, acne, hair loss
Progestins and progesterone	Provera/Prometrium/Aygestin	Increase risk of heart disease
Medical therapy for insulin resistance and diabetes		
Insulin-sensitizing drugs	Metformin, thiazolidinediones	Nausea, abdominal bloating, vomiting, and loss of appetite
Insulin secretion drugs	Sulfonylureas, meglitinides, incretin mimetics	Weight gain, hypoglycemia
Insulin resistance	Corticosteroids - Rayos, orlistat	Weight gain, increased appetite
GLP-1	Bydureon, Byetta, Victoza	Headache, nausea, and diarrhea
Medical treatment for fertility		
Ovulation induction	Clomiphene citrate/metformin	Multiple births, ovarian cancer
Gonadotrophins	FSH/LH/hCG	Multiple pregnancies
Assisted reproductive technology	IVF	Cost and failure
Medical therapy for acne, hirsutism, and hair loss		
Antiandrogen	Androcur/Aldactone/Proscar	Birth defects, weight gain, depression
Sebum-reducing cream	Isotretinoin/Rogaine	Dry skin and eczema
Medical therapy for obesity		
Lipase inhibitors	Orlistat, Lorcaserin, Liraglutide	Risk for heart disease
Central nervous system stimulants/anorexiants	Belviq/Qsymia/Adipex/Regimex/Diethylpropion	Dizziness, diarrhea, anxiety, hair loss
Opioid receptor blockade	Naltrexone	Nausea, constipation
GLP-1	Victoza/Saxenda	Nausea, abdominal pain, constipation
Medical therapy for depression		
Antidepressants	Anafranil/Adapin/Aventyl/Elavil	Fatigue, weight gain, tremors, bladder problems
Antianxiety drugs	Tranquilizers - Xanax/Valium	Confusion, stomach upset, dizziness
Lifestyle management		
Diet	Wholegrain cereals, low glycemic index foods, less Na and sugar intake	-
Physical activity	Walk, running, aerobics	-
Natural supplements		
Herbs	Licorice root/Maca/Vitex/Chasteberry/inositol	-

GLP1=Glucagon-like peptide 1, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, hCG=Human chorionic gonadotropin

Eligibility criteria

Inclusion criteria

Studies meeting the following criteria were included: (1) cross-sectional, case–control, or cohort studies including PCOS women aged 15–45 years and age-matched controls of any ethnicity; (2) PCOS was diagnosed based on either Rotterdam, NIHCD, AES criteria, or all three; (3) studies containing original data (independent of other studies); (4) design where the prevalence of PCOS with sample size was presented; and (5) publications in full text written in English.

Exclusion Criteria

The studies were excluded, if these (1) contained data overlapping data with other studies (2) reported in language other than English (3)epidemiological studies reporting prevalence in family members of affected cases (4)letters, abstracts and conference proceedings ,which are not fully published in peer reviewed journals or published with limited access.

Data extraction

A data extraction form consists of information needed for the study (name of first author, year of publication, country, study design, study population size and description, age group, diagnostic criteria used, and prevalence rates). 95% confidence intervals (CIs) were calculated from the available data. The analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[35]

Quality assessment

The quality of included studies was assessed by QUADAS tool[36] (quality assessment for studies of diagnostic accuracy). The quality scoring checklist includes the following: (i) objective clearly stated, (ii) study design clearly described, (iii) patient selection criteria clearly defined, (iv) details of control selection, (v) sample size, (vi) method of PCOS diagnosis was provided, (vii) inclusion and exclusion criteria, (viii) prevalence clearly provided, (ix) confounding variables measured in the analysis, and (x) statistical analysis appropriately described. Studies scoring >7, 4–6, and <4 are rated as good, fair, and poor quality, respectively.

Results

Figure 1 outlines the detailed study screening and selection process. Database search yielded 2167 initial citations. All irrelevant studies (1136) were excluded. The studies describing other aspects of PCOS (polymorphism, prevalence of a particular comorbidity only, clinical trials, and reviews) were also excluded (551). A total of 480 articles had their full text reviewed for inclusion. Four hundred and seventeen articles were excluded after full-text review. Out of 68 included studies, 41 studies were omitted due to incomplete information. Twenty-seven prevalence involving 32,125 participants were therefore selected for inclusion in the review.

Baseline characteristics of studies

Table 3 provides a comprehensive portrait of the prevalence studies of PCOS across the globe including all three international diagnostic criteria.[27,37-64] The present review represented data based on random cross-sectional, prospective, cohort, case–control, and observational studies using all three different diagnostic criteria. The Rotterdam criteria are the most common one, included in 19 studies. The second most used criterion was NIH (11 studies). Twenty studies adopted cross-sectional study design. Only five studies include a large sample size (>1000). Southern China, Iran, and the USA reported a prevalence of 2.2%, 3%, and 4%, respectively. Beijing, Palestine, Brazil, Sri Lanka, the UK, Greek, and Spain found a prevalence rate in the range of 5%–10%. Australia, Turkey, and Denmark reported a higher prevalence (15%–20%). The prevalence rates differ with different criteria used. The Rotterdam criteria are the most acceptable diagnostic, as it includes broader evidences (oligomenorrhea/amenorrhea, clinical/biochemical hyperandrogenism plus polycystic ovaries) of PCOS. Studies adopting Rotterdam criteria as diagnostic methodology report higher prevalence rates when compared with the other two methods [Figure 2]. Today, 1 in every 10 women is diagnosed with PCOS across the world. Until the late 1990s, the studies regarding the prevalence of PCOS were rare. Most of the studies were carried out on small sample size. The number of random community surveys is also limited. Fourteen studies were conducted in Asia, with India being the country presenting maximum number of researches (five). Seven studies were conducted in Europe, two in Australia, one in Africa, two in North America, and one in South America [Figure 3].

Table 4 shows a comparison between the results of various PCOS-associated parameters using three different methods. The total number of PCOS patients included in these studies was 3434, 838, and 410 using RC, NIH, and AES criteria, respectively. Statistically significant differences were observed in polycystic ovaries on ultrasound (0.003%), hirsutism (0.001), and obesity (0.001) among PCOS cases when all three diagnostic criteria were compared. As expected, overall PCOS cases had

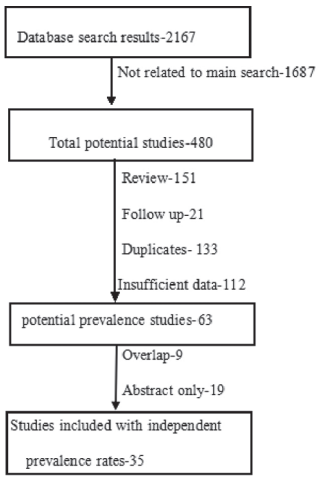

Figure 1: Flowchart of study screening and selection procedure

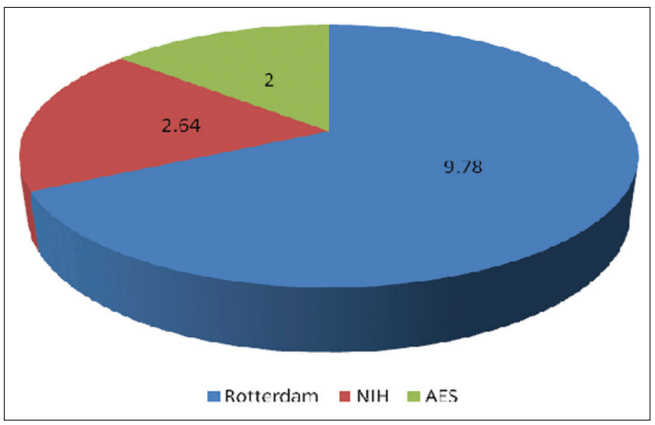

Figure 2: Prevalence (%) of PCOS using different diagnostic criteria. PCOS=Polycystic ovary syndrome, NIH=National Institutes of Health, AES=Androgen excess society

Table 3: Prevalence studies of PCOS across the globe with different diagnostic criteria

(a) Random community-based prevalence of polycystic ovary syndrome across the globe

Place	Population	Participant selection	Age	Criteria	Prevalence (95% CI)	Reference	QS
Prevalence studies with cross-sectional study design							
India	385	City	17-24	RC	8.2% (±2.74)	Gupta M *et al*., 2018	8
India	480	University	NR	RC	8.1% (±2.76)	Joseph N *et al*., 2016	7
Rohtak, India	325	Random	16-45	RC	6.8% (±2.74)	Deswal R *et al*., 2014	8
India	600	Census block	15-24	RC	22.5% (±3.34)	Joshi B *et al*., 2014	8
				AES	10.7% (±2.47)		
Mumbai, India	778	Census block of Mumbai	15-24	RC	22.5% (±2.93)	Srabani M *et al*., 2014	8
				AES	10.7% (±2.17)		
Denmark	863	Hospital	20-40	RC	16.6% (±8.48)	Lauritsen MP *et al*., 2014	7
Kerala, India	200	Medical college	18-31	RC	15% (±4.95)	Vijayan CP *et al*., 2013	8
Palestine	137	University	18-24	NIH	7.3% (±4.36)	Musmar S *et al*., 2013	8
Ankara, Turkey	392	Female staff	18-45	NIH	6.1% (±2.37)	Yildiz BO *et al*., 2012	9
				RC	19.9% (±3.95)		
				AES	15.3% (±3.56)		
Darwin, Australia	248	Indigenous women	15-44	NIH	15.3% (±4.48)	Boyle JA *et al*., 2012	8
Salvador, Brazil	859	Women seeking primary health care	18-45	RC	8.5% (±1.86)	Gabrielli L, 2012	8
Kerman, Iran	118	Women with acne	14-38	NIH	60.2% (±8.83)	Zandi S *et al*., 2010	7
				Ultrasonography	8.3% (±9.02)		
Isfahan, Iran	1000	Females visiting premarriage screening clinic	14-18	MI and H	3% (±1.06)	Hashemipur M *et al*., 2004	7
Greek island, Lesbos	192	Random	17-45	H and OM	6.77% (±3.55)	Diamanti KE *et al*., 1999	8
Prevalence studies with community-based study design							
Beijing	15,924	Han Chinese women in community	19-45	Rotterdam	5.6% (±0.36)	Rong Li *et al*., 2013	8
Lucknow, India	1520	Volunteer college girls	18-25	MI or H or both	3.7 % (±0.95)	Gill H *et al*., 2012	8
Iran	1126	Random selection	18-45	NIH	7.1% (±1.50)	Tehrani FR *et al*., 2011	8
				AES	11.7% (±1.88)		
				RC	14.6% (±2.06)		
Sri Lanka	3030	Random community selection	15-39	RC	6.3% (±0.87)	Kumarapeli V, 2008	9

(b) Prospective, observational, and case-control prevalence studies of polycystic ovary syndrome

Place	Population	Participant selection	Age	Criteria	Prevalence (95% CI)	Author, year	QS
Prevalence studies with prospective study design							
India	460	College girls	15-18	RC	9.13% (±2.63)	Nidhi R *et al*., 2011	7
UK	400	Women visiting University of Alabama	18-45	RC	6.6% (±2.43)	Azziz R *et al*., 2004	9
Spain	154	Caucasian women in blood donation camp	18-45	NIH	6.5% (±3.89)	Asuncion M *et al*., 2000	7

Contd...

Table 3: Contd...

(b) Prospective, observational, and case-control prevalence studies of polycystic ovary syndrome

Place	Population	Participant selection	Age	Criteria	Prevalence (95% CI)	Reference	QS
Alabama	369	White and non white women	18-45	RC	4% (±2.00)	Knochenhauer ES *et al*., 1998	8
Prevalence studies with observational study design							
USA	100	Self-reporting women with PCOS	18-45	NIH	53% (±9.78)	Clark NM *et al*., 2014	6
				RC	70% (±8.98)		
				AES	62% (±9.51)		
Tanzania	100	Infertile women in hospital	18-45	RC	32% (±9.14)	Pembe AM *et al*., 2009	7
Germany	61	Female-to-male transsexuals	18-45	NIH	11.5% (±8.01)	Schötz SN, 2009	6
				RC	14.8% (±8.91)		
China	915	Medical examination center	18-45	RC	2.2% (±0.95)	Chen X *et al*., 2008	7
Prevalence studies with cohort study design							
Thailand	58	Women with idiopathic intracranial hypertension	18-45	NIH	15.5% (±9.31)	Avisar I *et al*., 2012	8
Australia	728	Maternity hospital	27-34	NIH	8.7% (±2.05)	March WA *et al*., 2010	7
				RC	11.9% (±2.35)		
				AES	10.2% (±2.20)		
Rotterdam, Utrecht	869	WHO-II normogonadotropic, anovulatory infertility women in medical center	18-45	NIH	55% (±3.31)	Broekmans FJ *et al*., 2006	7
				RC	91% (±1.90)		
Prevalence studies with case control study design							
New Delhi, India	175 with CLT and 46 control	Girls with euthyroid CTL	13-18	RC	46.8% (±7.39)	Ganie MA, 2010	7

CI=Confidence interval, NIH=National Institutes of Health, RC=Rotterdam criteria, AES=Androgen excess society, CLT=Chronic lymphocytic thyroiditis, QS=Quality score

higher percentages of girls with oligomenorrhea. Infertility was significantly higher in women with polycystic ovary morphology (21.70%) using AES criteria, while Rotterdam criteria reported the presence of the same in minority of women (6%). Hirsutism was present among 58.12% of cases (Rotterdam diagnosis) and 52.68% of cases (AES diagnosis). Degree of hirsutism was less in women diagnosed with NIH criteria (25.77%). However, there was no statistical difference found in the prevalence of insulin resistance and metabolic syndrome profile of these women. PCOS is present in both obese and lean females. Rotterdam criteria report a low prevalence of insulin resistance (8.04%) as the condition was found to be more prevalent in obese PCOS cases.

Discussion

PCOS is associated with multiple reproductive, reproductive, and psychological complications which are of serious concern. PCOS represents a significant socioeconomic burden to health care. It was during the mid-nineteenth century that headway was made in the understanding of PCOS by Stein and Leventhal. In India, it took almost a century for the prevalence of PCOS to come in the forefront in medical literature. To address this issue, few nationally representative surveys have been conducted in India from 2010 to 2014, reporting the variation in prevalence rate from 6% to 46.8%. Ganie *et al*. published the first Indian case–control study using Rotterdam criteria in 2010, which reported a high prevalence rate of 46.8% as

Table 4: Different characteristics of polycystic ovary syndrome patients

Complications	Criteria - RC (*n*=3434), *n* (%)	Criteria - NIH (*n*=838), *n* (%)	Criteria - AES (*n*=410), *n* (%)	*P*
MI				
Oligomenorrhea	3021 (88.21)	680 (81.21)	340 (83.09)	0.001
Amenorrhea	397 (11.57)	158 (18.85)	67 (16.34)	0.060
Infertility	217 (6.33)	104 (12.41)	89 (21.70)	0.040
Polycystic ovaries	869 (25.31)	-	97 (23.65)	0.003
Hirsutism	1995 (58.12)	216 (25.77)	216 (52.68)	0.001
Obese	1863 (54.26)	446 (53.22)	229 (55.85)	0.001
Nonobese	1570 (45.73)	392 (46.77)	194 (47.31)	0.066
Insulin resistance	276 (8.04)	180 (21.47)	106 (25.85)	0.240
Metabolic syndrome	206 (6.01)	57 (6.80)	19 (4.63)	0.110

Distributions were compared using analysis of variance. Categorical variables were compared using Pearson's Chi-square test. $P<0.05$ is considered statistically significant. RC=Rotterdam criteria, MI=Menstrual irregularities

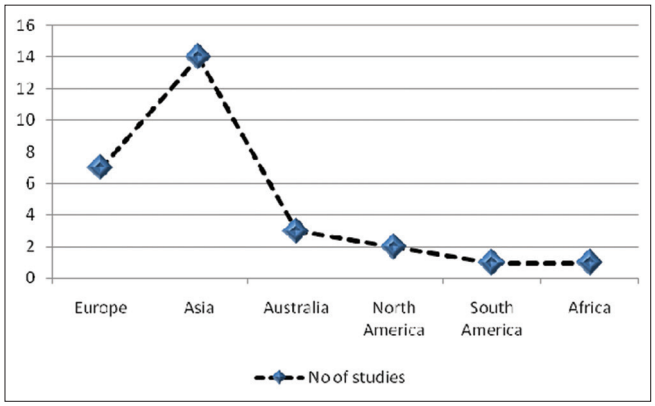

Figure 3: Scenario of prevalence studies in the world

the study was conducted in 176 chronic lymphocytic thyroiditis (CLT) patients.[64] Nidhi *et al*., in 2011, conducted a prospective study involving 460 girls of 15–18 years from a residential college in South India and reported a prevalence rate of 9.13%.[54] A 2017 study conducted by Gupta *et al*. in 500 college girls aged 17–24 reported a prevalence rate of 8.2%.[37] Later, during 2017, Choudhary A *et al*. showed a higher prevalence of 41% in 170 women with menstrual irregularities by NIH criteria. Another study conducted in Mumbai among 600 girls of 15–24 years reported an estimated prevalence of 22.5%.[40] A meta-analysis conducted by Ding *et al*., in 2017, reviewed the prevalence of PCOS across different ethnic groups and concluded that Caucasian females are less likely to develop PCOS compared with middle east and non white female populations.[65] Accordingly, the prevalence of PCOS varies among different countries worldwide. Iran, China, and the USA reported a prevalence of 3%, 2.2%, and 4.7%, respectively. Brazil, Beijing, Sri Lanka, Palestine, Greece, the UK, and Spain found a prevalence rate in the range of 5%–10%. Denmark, Turkey, and Australia reported a higher prevalence range (15%–20%). In 2018, Wolf *et al*. reported the prevalence of PCOS in Mexico also.[66] In 2019, Ganie *et al*. concluded the prevalence of PCOS in India ranging from 3.7%–22.5% depending on the population studied and criteria used for diagnosis.[67] A report from this laboratory showed that overall 71% of the women with PCOS resided in urban regions, while 29% in rural regions in the Haryana state of India.[68] The discrepancies might be partly attributed to small sample sizes, socioeconomic differences, clinical heterogeneity, low statistical power, differing ethnic backgrounds among various populations, geographic variations, and interactions with other environmental plus genetic factors. Until today, five different GWASs have identified 16 candidate genes/loci associated with PCOS. These findings implicated the role of genes involved in gonadotropin action (LHR and FSHR), insulin signaling and type 2 diabetes (INSR, THADA, HMGA2), cell proliferation (YAP1 and SUMO1P1), and chromatin remodeling (TOX3) in the pathogenesis of PCOS.[15-19] Shim *et al*., 2015, conducted pathway-based GWAS to elucidate significant biological pathways and candidate genes involved in pathogenesis of PCOS.[20] The study identified three top rank pathways (ovulation, insulin secretion, and calcium signaling) associated with PCOS. INSR gene was observed in all three pathways. Variations in INSR gene could result in abnormal insulin regulation and disordered glucose homeostasis which enhances insulin resistance, type 2 diabetes, and obesity deteriorating metabolic profile of PCOS. To offer novel insights into the etiology, pathogenesis, and treatment of PCOS, future population-based prospective case–control studies in compliance with family-based linkage studies involving a large number of individuals in various populations are clearly warranted. CLT is known as chronic lymphocytic thyroiditis. Ganie *et al*.[64] have reported that 170 girls (46 years age) with euthyroid CLT had higher hirsutism score, the lower number of annual menstrual cycles as well as higher insulin resistance score as compared to control girls, under the high prevalence of PCOS.

Conclusion and Future Perspectives

It is undoubtedly one of the most perplexing disorders posing threat to women's health, probably due to various manifestations of the disorder and lack of uniformly accepted diagnostic criteria. The pathogenesis of PCOS remains elusive, with contributions from insulin resistance, adipose tissue dysfunction, abnormal steroidogenesis, and hypothalamic–pituitary–ovarian dysregulation. Genetic variants and epigenetic environmental factors probably contribute to the dysregulation of these varied systems and raise new avenues of research investigation in the rapidly evolving field of PCOS. Despite rigorous research, certain questions are still unanswered so far. (i) As no single candidate gene has emerged as a convincing biomarker, so the future studies could be focused on selecting the appropriate genes as biomarkers for PCOS (ii) designing different therapeutic approaches to ameliorate additional complications such as metabolic syndrome, endometrial cancer, cardiovascular diseases, and mental health issues in later life; (iii) formulation of epigenetic studies to untangle the nature and nurture of the syndrome; (iv) need for globally agreed upon consensus on optimal diagnosis and management of PCOS; (v) conducting the large epidemiological studies worldwide to address the accurate burden of PCOS (vi) study of genetic polymorphism at wide scale to optimize individualized treatment; and (vii) increased awareness of PCOS and associated comorbidities to helps in early detection and management of PCOS. The possible roles of autoimmune phenomenon in the etiopathogenesis of PCOS and overexpression of certain genes of gonadotropin and neuroendocrine action, ovarian androgen biosynthesis, and insulin action in etiology of PCOS are suggested.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Differential diagnostic guidelines for diagnosis of polycystic ovary syndrome in adults and adolescence

Adult	Adolescence
Phenotype I: NIH criteria	AUB
Clinical and/or biochemical HA	Abnormal for age
Oligoanovulation	Persistent symptoms for 1-2 years
Phenotype II: RC	HA
Clinical and/or biochemical HA	Persistent testosterone elevation above normal levels
Polycystic ovary	
Oligomenorrhea/amenorrhea	Moderate-to-severe hirsutism
	Moderate-to-severe acne vulgaris to indicate HA
Phenotype III: AES	
Clinical and/or biochemical HA	

AUB=Abnormal uterine bleeding, HA=Hyperandrogenism, NIH=National Institutes of Health, RC=Rotterdam criteria, AES=Androgen excess society