

Review Article

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Epidemiology, pathogenesis, genetics & management of polycystic ovary syndrome in India

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder predominantly affecting women of reproductive age. Clinical manifestations are diverse including hyperandrogenism, anovulation, infertility and increased risk of metabolic diseases besides psychosocial dysfunction. This review provides information on the problem of PCOS in India, its pathophysiology, genetics and an overview of current management options to instigate further research in this field. Prevalence of PCOS in India ranges from 3.7 to 22.5 per cent depending on the population studied and the criteria used for diagnosis. Abnormalities in leptin-adiponectin (adipocyte biology), oxidative stress and autoimmunity are among the mechanisms studied regarding pathogenesis of PCOS. Many candidate gene studies have shown associations with PCOS in various studies. Studies have consistently demonstrated the relationship between the well-known manifestation of hyperandrogenism among Indian PCOS women and the metabolic morbidities including insulin resistance, glucose intolerance and cardiovascular risk. Management of individual components of PCOS can be achieved by medications or surgical methods, though further clarification regarding pathogenesis of PCOS is needed to sharpen our therapeutic armamentarium.

Key words Epidemiology - genetics - India - management - pathogenesis - pathophysiology - polycystic ovary syndrome - prevalence

Introduction

Polycystic ovary syndrome (PCOS) is considered to be a multifaceted disease with a spectrum of manifestations affecting not only women of childbearing age, but also adolescents and postmenopausal women¹. PCOS, by the nature of the disease, adversely influences the fertility and reproductive health of the affected women²; moreover, with its association with other lifestyle diseases, it is also

the cause of significant cardiovascular and metabolic morbidity³. The exact aetiology and pathogenesis of PCOS are still an area of active research, although multiple hypotheses have been postulated, ranging from genetic susceptibility to environmental exposure, both *in utero* and in the postnatal life⁴. Data on the genetics, metabolic parameters and clinical aspects of PCOS in Indian women are available. This article was aimed at reviewing the literature related to the

pathogenesis, epidemiology and genetics of PCOS in India, and biochemical and hormonal abnormalities in this disorder besides providing a brief overview of the management options.

Evolution of PCOS as a distinct syndrome - A historical overview

PCOS, discovered by Stein and Leventhal⁵, earned its name based on the ovarian morphology. The authors described seven women who shared the common features of menstrual disturbances, hirsutism and enlarged ovaries with many small follicles⁵. They also suspected that bilateral cystic ovaries were the result of abnormal hormonal stimulation, which was confirmed by the later investigators. Medical treatment became the preferred treatment over surgical resection of the ovaries when options such as clomiphene and follicle-stimulating hormone (FSH) became available⁶. There was a renewed interest in the surgical treatment of PCOS when laparoscopic treatment became popular. Newer technologies such as ultrasound to image ovaries were a breakthrough in the history of PCOS, and the ease of this technique made the diagnosis of PCOS simpler. However, this had the unexpected result that many women were diagnosed with mild or no other features of PCOS, but had polycystic ovaries⁷. This led to the term of polycystic ovarian morphology, the significance of which is still a subject of debate. It has been argued that the widespread acceptance of the Rotterdam criteria⁸, which included oligo-anovulatory women with polycystic ovarian morphology without clinical or biochemical evidence of hyperandrogenism, is premature and will lead to unnecessary diagnosis, laboratory evaluation and probably lifelong implications in these women⁹. Even after so many years of the recognition, the exact aetiology of this syndrome remains elusive and is now considered to be multifactorial, with a strong genetic component. Although insulin resistance (IR) is consistently found in women with PCOS, yet it is not included in any diagnostic criteria.

Clinical features, comorbidities and diagnostic criteria of PCOS

The clinical manifestations of PCOS include oligomenorrhoea, hirsutism, excessive acne and hair loss. In adolescence, it causes significant psychiatric disturbances such as anxiety and depression. PCOS is the leading cause of anovulatory infertility in women. The metabolic consequences include impaired glucose tolerance, type 2 diabetes, obesity and increased risk of cardiovascular diseases. Metabolic complications and increased cardiovascular morbidity were found to be more in the classic PCOS compared to other phenotypes, even after adjustment for obesity¹⁰. Clinicians now have these three sets of criteria (Table I) to choose from, though the Rotterdam criteria⁸ are found to be more preferred. The National Institutes of Health (NIH) Evidence-based Methodology Workshop in 2012 published the final report¹³ which stated that the following specific phenotypes (Table II) should be reported explicitly in all research studies.

Epidemiology of PCOS in India

Only a few researchers have studied the prevalence of PCOS in India and among those, most of the sampling was convenience based, which might not reflect the true status of PCOS prevalence in the community. A pilot cross-sectional study conducted in Tamil Nadu assessed young adolescent females and found a prevalence of 18 per cent for PCOS¹⁴. They also concluded that the proportion of PCOS was higher in urban women in comparison to the rural women. A similar study conducted in Mumbai, which was an urban community-based study, found that the prevalence of PCOS was 22.5 per cent by the Rotterdam criteria and 10.7 per cent by the Androgen Excess Society criteria¹⁵. A study conducted among medical students at a private medical college in south India using the modified Cronin questionnaire¹⁶, which included 10 items, found that PCOS was a common disorder among the participants and reported a high

Table I. Diagnostic criteria of polycystic ovary syndrome (1990-2009)

PCOS definition	Clinical hyperandrogenism or biochemical hyperandrogenism (elevated total/free testosterone)	Oligomenorrhoea or oligo-anovulation	Polycystic ovaries on ultrasound
NIH (1990) ¹¹	Yes	Yes	Not included
ESHRE/ASRM Rotterdam (2003) ⁸ 2 of 3 criteria	Yes/no	Yes/no	Yes/no
AE-PCOS Society (2006) ¹²	Yes	Yes/no	Yes/no

PCOS, polycystic ovary syndrome; AE, androgen excess; NIH, National Institutes of Health; ASRM, American Society for Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology

incidence of mood disorders among them¹⁶. A study from Lucknow was published, in which college-going women with menstrual irregularity and hirsutism, in the age range of 18-25 yr, were studied, and it was reported that the calculated prevalence using the NIH criteria, among the participants, was only 3.7 per cent¹⁷. Another study from Andhra Pradesh studied young women from a residential college and found that 9.13 per cent of them satisfied the Rotterdam criteria for PCOS¹⁸. Vidya Bharathi *et al*¹⁹ showed that the prevalence of PCOS diagnosed by the Rotterdam criteria in community-dwelling women from rural and urban areas of Chennai was 6 per cent. International studies report the prevalence of PCOS to be in the range of 4-10 per cent of women of reproductive age²⁰. As the prevalence of PCOS has been found to be higher or lower depending on the criteria used in these studies, which might be the obvious reason for the discrepancy in the prevalence rates among the studies from India, it is difficult to draw a clear conclusion. Hence, from the limited data available, it can be said that the prevalence

of PCOS in India ranges from 3.7 to 22.5 per cent (Table III).

Pathophysiology and genetics of PCOS

PCOS is a disease with a complex multipronged pathogenesis which is still under investigation (Figure). The various pathogenetic mechanisms of PCOS include abnormal gonadotropin-releasing hormone (GnRH) regulation leading to increased luteinizing hormone (LH) and decreased FSH; decreased response of ovarian follicles to FSH; increased anti-Mullerian hormone (AMH); follicular arrest and increased secretion of testosterone, estradiol and dehydroepiandrosterone (DHEA). Obesity, especially abdominal fat deposition, is the major predisposing factor for the expression of IR and metabolic phenotype in PCOS²². Thus, IR at post-receptor level and adipocyte dysfunction are responsible for the metabolic consequences of

Table II. Phenotypes of polycystic ovary syndrome as per the Rotterdam criteria⁸

Frank or classic polycystic	All the three - chronic anovulation, polycystic ovaries and hyperandrogenism
Classic non-cystic	Anovulation, hyperandrogenism with normal ovaries
Non-classic ovulatory	Regular menses, polycystic ovaries and hyperandrogenism
Non-classic mild or normo-androgenic	Anovulation, polycystic ovaries with normal androgens

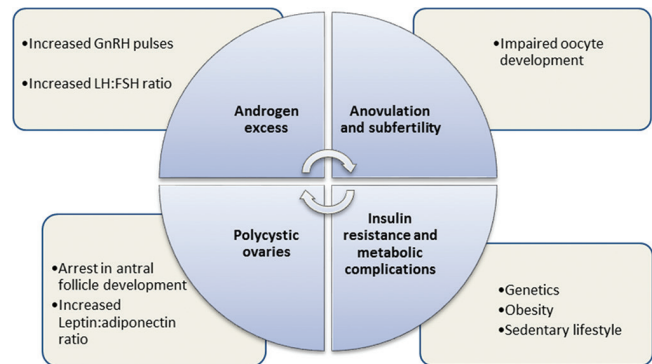


Figure. Current concept of pathophysiology of polycystic ovary syndrome. LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone. Source: Ref 21.

Table III. Prevalence studies on polycystic ovary syndrome in Indian women/girls

Study	n	Place/yr	Population/sampling	Prevalence per cent (criteria)
Balaji <i>et al</i> ¹⁴	126	Tamil Nadu/2015	Young adolescents (12-19 yr) Urban and rural	18 (Rotterdam) ⁸
Joshi <i>et al</i> ¹⁵	600	Mumbai/2014	Adolescents and young adolescents (15-24 yr) Community based	22.5 (Rotterdam) ⁸ 10.7 (AES) ¹²
Joseph <i>et al</i> ¹⁶	441	Karnataka/2016	Medical and dental college students (20.4±1.5 yr) with either menstrual irregularity or hirsutism	9.1 (modified version of Cronin questionnaire) ¹⁶
Gill <i>et al</i> ¹⁷	1520	Lucknow/2012	College girls (18-25 yr) with menstrual irregularity and hirsutism	3.7 (NIH criteria) ¹¹
Nidhi <i>et al</i> ¹⁸	460	Bengaluru/2011	College girls (15-18 yr) Oligomenorrhoea and/or hirsutism	9.13 (Rotterdam) ⁸
Vidya Bharathi <i>et al</i> ¹⁹		Chennai/2017	Random general rural and urban population	6 (Rotterdam) ⁸

AES, Androgen Excess Society

PCOS²¹⁻²⁵. Many other biochemical and hormonal aspects apart from the widely known pathophysiological mechanisms underlying PCOS have been studied by Indian researchers and are reviewed in detail below.

Studies on PCOS pathogenesis from India

Role of leptin and adiponectin in PCOS pathogenesis

Leptin is a major intermediary between nutritional status and reproductive health of women. High levels of leptin have been found to be associated with the markers of IR in PCOS patients^{24,26}. After adjusting for potential confounders such as obesity status, PCOS women had higher leptin levels as compared to controls and leptin also was positively correlated with the serum testosterone levels²⁷. Another study also demonstrated that high leptin in PCOS women was independent of the obesity status, but this study did not find a significant correlation between leptin levels and serum testosterone²⁷. From these case-control studies, it is difficult to ascertain the cause and effect relationship between leptin levels and hyperandrogenemia or PCOS phenotype, though it is imperative that the complex nature of the same needs further exploration. Singh *et al*²⁸ in a case-control study 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 women had low adiponectin, which improved with metformin treatment. Independent of obesity status, hypoadiponectinemia correlated with IR and hyperandrogenemia; this may be because lean PCOS women also may have intra-abdominal fat and thus unhealthy metabolic profile. Reiterating the role of adiponectin in PCOS pathogenesis, animal studies showed that adiponectin treatment reduced androgen synthesis in DHEA-treated PCOS mice in an *in vitro* study²⁹. In another case-control study, plasma leptin:adiponectin ratio (L:A ratio) seemed to be positively associated with markers of metabolic syndrome and IR, thus reconfirming the lower adiponectin levels to be a potential biomarker of metabolic risk and IR in PCOS women³⁰.

Evidence from proteomics and metabolomics studies

In large case-control study on the proteomics of follicular fluid from women with PCOS and controls undergoing *in vitro* fertilization (IVF) treatment found altered levels of proteins involved in extracellular matrix remodelling, complement coagulation cascade, fibrinolysis, vasculature development, angiogenesis, lipid transport and metabolism, and the authors

postulated that it might reflect the molecular defects in folliculogenesis³¹. A study of the serum metabolomics of Indian women with PCOS during day 3 to 5 of their menstrual cycle using proton nuclear magnetic resonance and pattern recognition approach showed dysregulation in the expression of various metabolites in the serum of PCOS women, which indicated involvement of multiple pathways in amino acid metabolism, carbohydrate/lipid metabolism, purine and pyrimidine metabolism and protein synthesis³².

Role of oxidative stress and autoimmunity in PCOS pathogenesis

The role of oxidative stress in the pathogenesis of various reproductive diseases and conditions including infertility, recurrent abortions and pre-eclampsia has been postulated, and PCOS is no exception. Plasma amino acid levels were found to be significantly deranged (lower levels of methionine, cystine, isoleucine, phenylalanine, valine, tyrosine, proline, glycine, lysine and histidine and higher arginine and alanine levels) in PCOS women as compared to controls³³, and the authors suggested this to be a marker of higher metabolic and oxidative stress in PCOS women. Reduced arginine bioavailability was found in PCOS women, which correlated with low nitric oxide levels, increased oxidative stress and thus lowered regulatory T cells (Treg cells) in patients with PCOS³⁴. Krishna *et al*³⁵ demonstrated for the first time that the immunosuppressive action of CD4+CD25+CD 127-Treg cells was reduced in PCOS, and this might influence the reproductive function of these women adversely. Sumithra *et al*³⁶ studied the markers of oxidative stress and high sensitivity C-reactive protein levels (marker of cardiovascular risk), in patients with PCOS compared to controls, and found that both are significantly elevated in the PCOS cases. Deepika *et al*³⁷ studied genomic instability and cytotoxicity due to oxidative stress, assessed by estimating the frequency of micronucleated cells in epithelial samples and serum malondialdehyde levels, respectively, and found a positive correlation in patients of PCOS as compared to controls, which suggested high oxidative stress in PCOS women. Other investigators have specifically demonstrated elevated oxidative stress markers in lean PCOS patients³⁸. In oral contraceptive pill (OCP)-treated women, plasma intercellular adhesion molecule-1 (ICAM-1) and tumour necrosis factor- α (TNF- α) levels were significantly higher, compared to drug-naïve PCOS women, which suggested a pro-

inflammatory state in the OCP-treated women, despite reduced androgen and regularized menstrual cycles³⁹.

PCOS has long been suspected to have a component of autoimmune origin. Arora *et al*⁴⁰ from New Delhi found higher prevalence of antithyroglobulin antibodies in PCOS women and suggested a possible role of autoimmunity in the pathogenesis of PCOS. A small case series of patients with both PCOS and Grave's disease also suggested a possible autoimmune aetiology of PCOS⁴¹.

Other mechanisms proposed to have a role in PCOS pathogenesis

Some studies have suggested a role of vitamin D deficiency in metabolic abnormalities seen in PCOS women, but many authors have opined that hypovitaminosis D is ubiquitous in India, and this does not seem to alter the metabolic phenotype in women with PCOS^{42,43}. Altered mineral status in the form of hypercalcaemia and very low manganese levels in addition to higher levels of zinc and copper was demonstrated in women with PCOS compared to controls⁴⁴, which led the authors to propose that altered trace mineral milieu might play a significant role in the pathogenesis of PCOS. The various metabolic, inflammatory and autoimmune components including the obesity-related cytokines and oxidative stress markers evaluated in relation to the pathogenesis of PCOS highlight the multifaceted nature of this disorder and the need for further research to better delineate the contribution of each of these markers and mediators in the final expression of the syndrome of PCOS.

Genetics in PCOS

The evidence that PCOS may be genetically determined initially came from twin studies, where the incidence of PCOS was twice as high in women with an affected twin as compared to the rest of population⁴⁵. Candidate gene approach worldwide has identified many susceptibility genes including cytochrome P1A1 (*CYP1A1*), *CYP11A*, *CYP17A1*, *CYP19*, 17 β -hydroxysteroid dehydrogenase (*HSD17B6*), androgen receptor (*AR*), sex hormone-binding globulin (*SHBG*), insulin receptor (*INSR*), insulin receptor substrate 1 (*IRS1*), peroxisome proliferator-activated receptor gamma (*PPAR- γ*), follicle stimulating hormone receptor (*FSHR*), luteinizing hormone/chorionic gonadotropin receptor (*LHCGR*), anti-Mullerian hormone receptor type 2 (*AMHR2*), interleukin (*IL*) IL-1A, IL-1B and IL-6⁴⁵, whereas genome-wide association studies have identified many susceptibility

loci including THADA, DENND1A, LHCGR, FSHR, C9orf3, YAP1, GATA4, -NEIL2 and ERBB4^{23,46}.

Studies in the genetics of PCOS from India

Diabetes and metabolic syndrome-related genes

In a small study from Hyderabad, 15 single-nucleotide polymorphisms (SNPs) from nine type 2 diabetes-related genes (such as *TCF7L2*, *IGF2BP2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A*, *IRS1*, *CAPN10* and *PPAR- γ*) were studied in PCOS women and controls; no significant association was found; the authors cited studies from other ethnic populations and suggested that the non-association might be universal⁴⁷. Gly972Arg SNP of *IRS1* was found to have a positive association with PCOS in a south Indian study population, whereas *INS*, *IRS2*, *PPAR- γ* and *CAPN10* failed to show any association in the same study from Chennai⁴⁸. Insulin receptor gene polymorphism was studied later⁴⁹, for its association with IR in Indian women with PCOS; the study suggested that CC genotype (C1085T) might be developed as a marker for IR and metabolic complications in Indian women⁴⁸. Pro12Ala polymorphism of *PPAR- γ* showed significant association with reduced susceptibility for PCOS in a study published from Mumbai⁵⁰. The Calpain-10 (*CAPN10*) SNPs showed variable association with PCOS in the obese subgroup of patients⁵¹; the authors highlighted the importance of this gene in PCOS pathophysiology. The *IRS-1* and *PPAR- γ* gene polymorphisms were found to have a probable protective role against the development of certain specific PCOS sub-phenotypes⁵². Angiotensin-converting enzyme (ACE) I/D polymorphism was found to be associated with an early age at onset of PCOS symptoms in a case-control study from Hyderabad⁵³. A preliminary study on vitamin D receptor polymorphisms in PCOS patients and controls found no significant association, though some of the SNPs suggested a possible functional significance with regard to PCOS-specific clinical/biochemical traits⁵⁴. In a study conducted by Yousuf *et al*⁵⁵ among Kashmiri women with PCOS and controls, it was found that the *ICAM 1* gene polymorphism was not significantly associated with PCOS women compared to controls.

Ovarian function-related gene polymorphisms

In a study to investigate the association of Connexin37/Gap junction alpha 4 gene C1019T SNP with the susceptibility to PCOS among south Indian women⁵⁶, cases of PCOS were found to be significantly more associated with C/C and C alleles of the C1019T

SNP, compared to the controls. Another study⁵⁷ conducted among two ethnically different PCOS case-control groups has shown that 5,10 methylene tetrahydrofolate reductase (*MTHFR*) gene 677 CT polymorphism does not affect PCOS susceptibility in Indian women. The *LHCGR* gene polymorphism rs-2293275 was found to be significantly associated with PCOS compared to controls in a study⁵⁸ from Hyderabad. Another study from Hyderabad⁵⁹ suggested that vascular endothelial growth factor +405G/C polymorphism might constitute an inheritable risk factor for PCOS in south Indian women. Insulin-like factor 3 gene polymorphisms were studied among women from Mumbai⁶⁰, and the authors showed a significant association between rs6523 polymorphism and increased risk of PCOS. Follistatin gene exons were amplified and studied⁶¹ for mutations in a large cohort of PCOS women and controls from south India; the authors found no significant role of follistatin gene variants in PCOS susceptibility. Androgen receptor CAG repeat length polymorphism was reported to have no significant association with PCOS in a case-control study⁶².

Oxidative stress and cytokine-related gene polymorphisms

Two polymorphisms (L55M and Q192R) of paraoxonase 1 (*PON1*) gene were studied for their association with PCOS susceptibility and related traits in Indian women from Mumbai⁶³, and the authors found that one of those SNPs (L55M) was associated with reduced PCOS susceptibility only in lean women and that it also impacted features such as hyperandrogenemia, lipid parameters and glucose metabolism in these women. This led the authors to suggest that the genetic pathophysiology of PCOS was different in lean and obese women. In another study from south India⁶⁴, *IL* 6174 G/C SNP was found to be significantly associated with PCOS risk. A case-control study from south India on the polymorphisms of *TNF- α* gene and found that the distribution of genotypes for rs1799964 was significantly different between the groups⁶⁵. *IL- β* , *IL-1Ra* and *FABP1* gene variants were found to be significantly associated with many metabolic features of PCOS⁶⁶. Adiponectin and resistin gene polymorphisms were studied in south Indian women⁶⁷; while it showed no association of the former with PCOS, the authors suggested that resistin gene variants might have a role in PCOS susceptibility. Another study from Hyderabad has shown that carriers of PPAR- γ coactivator 1 α (PGC-1 α) rs8192678 'Ser' allele have increased risk of developing PCOS⁶⁸.

Miscellaneous genes associated with PCOS

In a study from Hyderabad, *CYP11A1* microsatellite (tttta)_n repeat polymorphism was found to be more common in PCOS patients as compared to controls⁶⁹, and the authors opined that because this cholesterol side-chain cleavage enzyme-encoding gene was instrumental in the synthesis of sex hormones, this could be a genetic marker of susceptibility to PCOS in the south Indian population studied. Leutinizing hormone β -subunit gene variants were studied among women⁷⁰ with PCOS from south India; although the ones found to have significant correlation were silent in nature, the authors suggested exploration of other significant polymorphisms in the hypothalamic-pituitary-gonadal axis⁷⁰. Plasminogen activator inhibitor 1 (PAI-1) 4G/5G polymorphism was found to be associated with risk for recurrent pregnancy loss and implantation failure²⁵. Sagvekar *et al*⁷¹ showed that altered global DNA hypomethylation in peripheral blood lymphocytes and granulosa cells was strongly associated with PCOS and recommended larger studies to shed light on such epigenetic modifications in the PCOS susceptibility.

Candidate gene polymorphism studies involving genes related to diabetes, metabolic syndrome, oxidative stress, cytokines, ovarian function *etc.*, have been conducted in the area of PCOS related genetic research in India. The limitations of candidate gene polymorphism studies in proving the association and the strength of the association need to be acknowledged. Genome-wide studies need to be planned in the future.

Clinical features and co-morbidities of PCOS

A clinical study⁷² reported that in PCOS subgroups, the phenotype with hyperandrogenism and regular menstrual cycles had higher IR and gonadotropic hormonal abnormalities compared to the subgroup which had patients with irregular menstruation. Another study demonstrated that hyperandrogenism, in the form of high testosterone values, correlated well with obesity and sleep-disordered breathing in PCOS women, and this might be one of the reasons for high cardiovascular morbidity in the PCOS patients⁷³. Hyperandrogenic phenotypes of PCOS were found to be more prone to metabolic complications as compared to the phenotypes with normal androgen levels⁷⁴.

PCOS occurs in both obese and non-obese women equally, although markers of IR are more common in obese women⁷⁵. Acanthosis nigricans (AN) was found to be present in more than half of the PCOS women examined in a study conducted at Manipal,

south India⁷⁶. The authors described an association of AN with a family history of diabetes in first-degree relatives in all of these patients. Cardiovascular autonomic function was tested in women with PCOS in a study from south India, which showed an imbalance in the sympathovagal output in patients as compared to controls, and the authors suggested that the altered autonomic function might predispose these patients to cardiovascular morbidity⁷⁷. The prevalence of abnormal glucose tolerance (AGT) detected by oral glucose tolerance test (OGTT) was found to be high (around 35%) in a large number of young Indian women with PCOS, and it was found that family history of diabetes was not a predictor of AGT in these women⁷⁸. Thus, studies from India have consistently demonstrated the relationship between the well-known manifestation of hyperandrogenism among Indian PCOS women and the metabolic morbidities including IR, glucose intolerance and cardiovascular risk in this population.

Management of PCOS

The management of PCOS is as complex as the condition itself. The management and treatment of PCOS include a healthy diet, regular physical activity, and medications, which address the associated manifestations and co-morbidities. PCOS management strategies mainly aim at resolving the four major components of PCOS including regularity of menstrual periods, control of hyperandrogenism (acne and hirsutism), management of infertility and IR along with its associated risk factors (type 2 diabetes mellitus, hyperlipidaemia, and obesity). Both non-pharmacological and pharmacological management strategies are important in the overall management of PCOS.

Non-pharmacological measures

Studies on non-pharmacological measures to treat PCOS are very limited in the Indian literature. In a study on reproductive-age women with PCOS, improvement in novel inflammatory cardiac risk markers such as hs-CRP was reported with lifestyle modification, although metformin was also given to the study participants⁷⁹.

Pharmacological treatment

In a randomized, single-blinded, dose-comparison study, Bhattacharya *et al*⁸⁰ reported that OCP containing 20 µg ethinyl estradiol (EE) with drospirenone had similar effects on free androgen index in PCOS women

as that containing 30 µg EE with drospirenone. The same authors had earlier studied⁸¹ a combination of EE with desogestrel and found significant improvement in hyperandrogenic parameters only during the first six months of treatment and further continuation was useless. A six-month, open-label, randomized trial by Ganie *et al*⁸², of low-dose spironolactone and metformin combination than either drug alone, showed the superiority of the former in terms of improved clinical parameters and compliance to treatment. A comparison of metformin and OCP (EE plus drospirenone) was done as a prospective observational study (n=46) over one year by Suvarna *et al*⁸³, and metformin alone was found to be equally effective in regularizing menstrual cycles and treating hyperandrogenism in Indian women with PCOS. Use of non-hormonal options *i.e.*, metformin and spironolactone, after a period of oral contraceptive use, was retrospectively studied by Kulshreshtha *et al*⁸⁴, in a small group of women with PCOS for regularization of their menstrual cycles. They concluded that 75 per cent of women achieved regular cycles with non-hormonal treatment within one year of stopping OCPs. Saini *et al*⁸⁵ have tried to develop metformin-loaded cationic niosomes amalgamated with thermosensitive gel for intravaginal use in PCOS patients.

Treatment of complications

Infertility

Meenakumari *et al*⁸⁶ studied the use of metformin in PCOS women with luteal-phase progesterone deficiency and reported improvement in the same after four weeks of treatment with metformin 500 mg thrice a day. A prospective randomized trial was conducted where letrozole and clomiphene citrate (CC) were compared in patients with PCOS and anovulatory infertility. After three cycles of treatment, both letrozole and clomiphene showed comparable ovulation rates, but endometrial response and pregnancy rates were better in the former group⁸⁷. In a randomized trial comparing metformin and CC, where the primary outcome was live birth rate (LBR), Kar and Sanchita⁸⁸ reported that the efficacy of metformin was similar to clomiphene in terms of LBR, and their combination gave the highest ovulation rate and LBR. Yanamandra and Gundabattula⁸⁹ conducted a retrospective study of women who failed ovulation induction for primary infertility and hence underwent diagnostic laparoscopy and hysteroscopy followed by ovarian drilling. They showed an enhanced conception rate (around 50%)

with laparoscopic ovarian drilling (LOD). In a small prospective cohort study, the author opined that LOD had no significant effect on AMH levels and thus ovarian reserve⁹⁰. However, as Mitra *et al*⁹¹ pointed out, use of this treatment in unselected cases of PCOS was not prudent owing to its potential risks such as iatrogenic adhesions and ovarian insufficiency. Moreover, many authorities have questioned⁹² the utility of LOD in infertility treatment citing lack of significant rates of clinical pregnancy in evidence-based reviews. Considering the adverse effects of LOD, medical treatment with rosiglitazone and CC was compared with LOD and CC in women with PCOS suffering from infertility in a prospective randomized trial⁹³, and the authors concluded that there was no significant difference in ovulation rate or pregnancy rate between the two groups. A retrospective analysis of four-year data at a tertiary care centre in north India was reported by Singh *et al*⁹⁴ where PCOS patients undergoing IVF cycle with long GnRH agonist protocol were compared with those on fixed GnRH antagonist protocol, and there was no significant difference in pregnancy rate or incidence of ovarian hyperstimulation syndrome between the two groups.

Obesity, diabetes and other co-morbidities

Kumar and Arora⁹⁵ reported the results of a randomized controlled trial (RCT) where they studied orlistat versus metformin for weight reduction and ovulation rates in obese PCOS women. Orlistat was equal to metformin in terms of achieving the outcomes of weight reduction and ovulation. They also noted that orlistat had a better side effect profile and was better tolerated than metformin in this trial population. In a retrospective study, the authors⁹⁶ reported that in women with PCOS with AGT measured by OGTT, six-month therapy with spironolactone and metformin had similar effects in reducing the glucose levels.

Use of unconventional and supplemental pharmacological treatment in PCOS and its complications

Supplementation of vitamin D on insulin sensitivity/resistance parameters in PCOS women was studied by Garg *et al*⁹⁷ in a double-blinded RCT, and they concluded that vitamin D at a dose of 4000 IU daily for six months had no significant effect on these parameters.

Conclusion

PCOS is a heterogeneous clinical syndrome with a multifaceted pathogenesis and is associated with

lifelong morbidity. The clinical manifestations of PCOS include oligomenorrhoea, hirsutism, excessive acne and hair loss. The estimated prevalence in India ranged from 3.7 to 22.5 per cent. The prevalence of PCOS was found to be higher or lower depending on the criteria used, which might be the obvious reason for the discrepancy in the prevalence rates among the studies. Considering the vast diversity in the population of India, large-scale community-based studies using internationally accepted criteria, in various geographic regions, are necessary to shed light on the actual prevalence of this disorder. The various metabolic, inflammatory and autoimmune components including the obesity-related cytokines and oxidative stress markers in relation to the pathogenesis of PCOS highlight the multifaceted nature of the disorder and the need for further research into the subject to better delineate the contribution of each of these markers and mediators in the final expression of PCOS. Management and treatment of PCOS included healthy diet, regular physical activity, and medications, which address the associated manifestations and co-morbidities. More randomized trials are needed to find the best treatment options for Indian women suffering from this condition.

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