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"STEIN-LEVENTHAL SYNDROME": CURABLE CAUSE OF INFERTILITY?

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Abstract

Stein-Leventhal syndrome also called Polycystic Ovary Syndrome (PCOS) is most common hormonal disturbance affecting 6%–20% of reproductive age women, considered multifaceted with spectrum of conditions including menstrual irregularities, acne, hair loss, obesity and hirsutism. Moreover, it is also the cause of adverse cardiovascular, metabolic, reproductive and psychological approaches for reduction in quality of life. This review will help females understand responsible factors for the incidence, its health consequences and management needed. The literature reviewed in this narrative article is obtained from various databases such as PubMed, Medline, EMBASE using MeSH - compliant keywords and consulting related books. References from year 2003 to 2021 were assessed and relatable information included. Studies conducted across country reflects high prevalence and irregular menses, hirsutism, acne, obesity, acanthosis nigricans, infertility and negative impact on quality of life. Large scale studies across country are necessary for actual status. Accurate diagnosis at young age is the key factor. Counselling young females should be done to spread awareness and remove stigma for better future. Females present with reproductive and metabolic manifestations along with potential of several co-morbidities and stigma associated with this condition remains neglected global issue. The syndrome has significant association with short and long-term health conditions, if untreated, lead complications. The goals of management are menstrual regularity, hyperandrogenism reduction, infertility management and insulin resistance resolution through non-pharmacological and pharmacological approaches.

Keywords: polycystic ovary syndrome; hyperandrogenism; oligomenorrhea; diagnostic criteria; clinical manifestations; PCOS management.

Introduction

Polycystic ovary syndrome (PCOS) is the most common hormonal disturbance which affects 6%–20% of reproductive - age women and has been the most debatable female endocrine disorder worldwide, with India being no exception [1,2]. It is defined as the association of elevated androgen levels with chronic anovulation without a specific underlying disease of the adrenal or pituitary glands [3]. The disorder can be morphological or biochemical – hyperandrogenism which is usually

presented as a clinical hallmark of PCOS [4,5]. In 1935, Irving F. Stein and Michael L. Leventhal presented a group of seven women with common features: oligomenorrhea or amenorrhea combined with presence of bilateral polycystic ovaries established during surgery. Three presented with obesity, whereas five showed signs of hirsutism. On performing bilateral ovary wedge resection, 90% females achieved regular menses and among them, 65% achieved pregnancy. Hence, PCOS is also termed as Stein – Leventhal syndrome [6,7]. Typically, identified during years of adolescence, it is considered to be a spectrum of conditions including menstrual irregularities (amenorrhea, oligomenorrhea, DUB), cystic acne, hair loss, obesity and hirsutism or its equivalents [8,9]. Moreover, there is contribution towards significantly adverse morbid approaches such as Cardiovascular - hypertension, obstructive sleep apnea; Metabolic – type 2 diabetes, insulin resistance, obesity, acanthosis nigricans; Reproductive – anovulatory infertility affecting around 90–95% of women [10], potential endometrial, and ovarian cancer. They can also present with a pregnancy-related complication, such as gestational diabetes or spontaneous abortion [9,11]. Also, many present with psychological disabilities including generalized anxiety, depression and eating disorders which become responsible factors for reduction in quality of life [12]. According to WHO statistics, PCOS affected 116 million (3.4%) women across the world which has progressed to at least 1 in every 10 women to have confirmed diagnosis of the syndrome worldwide [13]. In the last couple of years, the country has witnessed an increase in the prevalence of the disorder, especially in adolescents. Lack of knowledge and lifestyle changes are the major factors leading to this phenomenon [14,15]. However, based on the recruitment of patients, criteria used, and application of screening methods, there are few and mostly convenience - based – sampling studies on the country's prevalence which may hamper the true status [2,16]. In a study conducted in Mumbai among adolescents aged 15-24 years, the prevalence was noted to be 22.5% whereas, a cross-sectional study in Tamil Nadu found an 18% prevalence. Reports from Lucknow showed prevalence in college-going women aged 18-25 years was only 3.7% [11]. Another study done in Andhra Pradesh; the prevalence was 9.13% [16]. Hence, it can be attributed that PCOS prevalence varies between regions of the country with an estimated range of 3.7 – 22.5%. Also, the prevalence is more in women living in cities compared to women in towns and villages. This article aims to review few existing tools and their utility in diagnosing PCOS, its clinical significance and different management approaches.

1. Etiopathogenesis

PCOS is understood to be the multifaceted pathological change that is still under research to be proven [11]. The high incidence in recent years can be attributed to multiple hypotheses ranging from hereditary to lack of awareness associated with it both in utero and in postnatal life [11,17] (see Figure 1).

1.1 Intrauterine life

Experimental studies suggests that Intrauterine growth restriction (IUGR) during pregnancy can increase fetal exposure to excess androgens or glucocorticoids that might induce the development of symptoms along with deciding the phenotypic expression of PCOS during adolescence. However, the viability of this potential theory is mixed, supported by some research while other research indicates no such association [17,18].

1.2 Genetics

Many susceptibility genes, including cytochrome *CYP1A1*, *CYP17A1*, 17-hydroxysteroid dehydrogenase (*HSD17B6*), androgen receptor (AR), sex hormone-binding globulin (SHBG), insulin receptor substrate 1 (*IRS1*), follicle-stimulating hormone receptor (FSHR), luteinizing hormone receptor has been recognized through candidate gene method, while, genome-wide correlation findings identified some susceptibility locus, such as *LHCGR*, *FSHR*, and *ERBB4*, which all play a role in PCOS genetic inheritance [11,19]. To date, various literatures have supported that the risk of

PCOS incidence is largely attributed to family history – 40% of siblings and 35% of mothers of patients affected, with an autosomal dominant pattern, aggravated by various environmental factors [12,19].

1.3 Reproductive

Abnormal Steroidogenesis majorly influences thecal cytochrome P450c17(*CYP17*) work that possesses both 17α-hydroxylase as well as 17,20-lyase action which causes substantial intraovarian androgen excess resulting in characteristic functional ovarian hyperandrogenism condition, which in return, stimulates undue development for primordial follicles by hampering the necessary follicles' maturity towards the foremost follicle development, thus, being responsible for ovarian abnormalities [6,20].

1.4 Metabolic

It is reported that high leptin levels have been positively correlated with serum testosterone levels and plasma leptin: adiponectin ratio (L:A ratio) has a positive association with insulin resistance parameters, thus, validating the low ratio to be a probable biomarker, with central fat accumulation as the liable constituent for insulin resistance manifestation as well as for metabolic syndrome [5,11].Insulin Resistance (IR) defined as reduced glucose response to a given amount of insulin and consequent compensatory hyperinsulinemia is the most widely accepted explanation for the resulting metabolic defects [21]. In PCOS, IR affects skeletal muscles, adipose tissue, and the liver, whereas, due to hyperinsulinism, direct stimulation of steroidogenic ovaries and adrenal glands causes androgen secretion and reduced synthesis of SHBG in liver, leading to elevated levels of free, biologically active androgens. This excess of ovarian androgen production causes dysregulation resulting in premature follicular atresia and anovulation [10,22].

1.5 Environmental

Women during their daily chores, unknowingly, get exposed to certain chemicals known as endocrine disruptors (EDs), most commonly bisphenol-A (BPA) which have anti-estrogenic, anti-androgenic properties that interfere with feedback regulation, DNA methylation, neuroendocrine cells alternation. These EDs as result, contribute as causative factors either to unveil syndrome characteristics in genetically susceptible females or interrupt hormone homeostasis which deteriorates their fertility status [19,23]. Usually, a sedentary lifestyle and lack of physical activity cause generalized obesity and abnormal body fat distribution which do play as exacerbating factors for PCOS. The available data support that unhealthy habits like smoking, alcohol, and a diet with high carbohydrates, low fiber content and high trans fat often act as potential factors for syndrome [18].

1.6 Miscellaneous

The significantly deranged plasma amino acid levels of cysteine, phenylalanine, glycine, tyrosine, etc., along with a large concentration of arginine is often highlighted as a parameter for metabolic and oxidative stress in PCOS [11]. During the onset of puberty, when females witness sudden changes in their menstrual cycles, excessive weight gain, acne, and overall physical appearance, it leads to confusion, and stress and acts as a contributing factor to a psychological dilemma. Lack of awareness and undiagnosed or inappropriate medical therapy often leads to 'PCOS Negative Impact' resulting in a high risk of anxiety, severe mood swings, depression, and even sometimes, suicidal tendencies [24,25].

2. Histopathology

Under gross description, the ovaries are twice in size, thick capsule with pearly white color and increased ovarian volume of more than 10 cm^3. There is the presence of numerous (>12) subcortical cysts which represent immature follicles, measuring around 2-9 mm in diameter and giving a crowded appearance around the cortex. Also, the endometrium may show metaplastic changes resembling

adenoacanthoma or adenocarcinoma [26,27]. On microscopic examination, the multiple cystic follicles are covered by dense thickening of tunica albuginea. There is luteinization of the theca interna causing stromal hypertrophy. Follicular cysts at different stages of maturation and atresia are seen [26,27].

3. Types of PCOS

PCOS is classified based on observed clinical features in females. Type A and Type C are noted to be the most common phenotypes with Type A being the most severe [28] (See Table 1).

Methods

1. Search strategy

We used PubMed, Medline, and EMBASE, to conduct our research. Search terms used included (polycystic ovary syndrome) OR (Stein-Leventhal syndrome) OR (Rotterdam criteria) OR (hyperandrogenism) OR (anovulation) OR (PCOS AND pathophysiology) OR (PCOS in India) OR (PCOS AND OCPs) OR (PCOS AND clinical features) OR (PCOS management). Results were limited to studies published between 2003 and 2021 and studies were included in the review if they were published in English. Additional relevant research was found by individually searching the sources of the included publications.

2. Study selection

In this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29] method was used. Certain observational studies, reviews, various original scientific research papers and studies that depicted a co-relation between polycystic ovary syndrome and various treatment approaches were included. After the removal of duplicates, there were 100 articles left for review. Titles and abstracts were screened for all 100 articles, leaving 23 articles left for review. Full text review was performed on all 23 articles; 05 articles met the full eligibility criteria. Only the most recent articles were considered for this review. A flowchart showing the methodology and study selection is presented in Figure 2 [29].

Current state of knowledge

Results

PCOS females mainly present with reproductive and metabolic manifestations along with the potential risk of leading several co-morbidities. (See Table 2).

1. Reproductive manifestations

Menstrual Disturbances manifest as oligomenorrhea, amenorrhea or dysfunctional uterine bleeding in around two-thirds of young females with PCOS mainly due to elevated LH levels coupled with androgens and insulin along with low FSH level [30]. Also, this hormonal imbalance by ovaries can lead to the presence of tiny cysts on the surface of large-sized ovaries along with hair, skin features and anemia [4,31]. Thus, PCOS is the causative factor for anovulatory infertility, or in some cases of pregnancy in PCOS women, it possesses as risk factor for suffering spontaneous abortion or developing gestational diabetes [6]. Skin and Hair characteristics are the most visible changes in this syndrome mainly caused due to excessive production of androgens and insulin [4]. Hirsutism defined as the appearance of excessive hair growth in the male pattern on androgen-dependent sites of the body is recognized as a classic feature and present in two-thirds of cases [32]. It is evaluated as per Ferriman - Galleway classification through which the result of hair growth > 8 suggest a positive sign. Other hirsutism equivalents include seborrhea, excess acne, alopecia, and hyperhidrosis as cutaneous signs of hyperandrogenism [32]. It is believed that irregular menses persist in the first few months and acne is quite common during adolescence, thus, progressive hirsutism is regarded as a good marker in PCOS diagnosis [4].

2. Metabolic manifestations

Studies have hypothesized that obesity acts synergistically as well as independently leading to the development of insulin resistance (IR) which presents Acanthosis Nigricans (AN) as a cutaneous sign, defined as dirty looking raised velvety, mossy, hyperpigmented skin condition, commonly found in body folds around the neck, armpits, groin, and breast and is considered an indicator for the severity of hyperinsulinemia along with hyperkeratosis and papillomatosis as histological characteristics [4,10,33]. It also leads to impaired glucose tolerance with an intense craving for carbohydrates, type 2 DM, and abnormal lipid profile [12]. Hyperandrogenism also causes sleep-breathing disorders leading to an increased risk of cardiovascular morbidity which is often predicted through levels of plasma gamma-glutamyl transferase (GGT) [10]. Hyperandrogenism also causes sleep-breathing disorders leading to an increased risk of cardiovascular morbidity which is often predicted through levels of plasma gamma-glutamyl transferase (GGT) [10].

Discussion

1. Diagnostic criteria

PCOS is regarded as the 'diagnosis of exclusion', thus, the approach includes screening, presence and source of excess androgen levels and laboratory investigations [32,33] (see Table 3).

1.1 Screening of individuals

It is necessary in cases involving - failure to establish a normal menstrual cycle after 2 years of menarche; pre-pubertal acne being resistant to standard treatment modalities or requires isotretinoin management; hirsutism associated with menstrual irregularities or accelerated obesity; central fat distribution with violaceous striae or family history of metabolic syndrome or type 2 DM [32].

1.2 Presence and source of androgen excess

Total testosterone level above 90 ng/dl is reliable for androgen excess. Moreover, free testosterone which is the fraction of plasma testosterone that is bound to albumin is the best single indicator because of its suppression by androgen excess and insulin resistance [32]. The most discriminating criterion for typical PCOS is adrenocortical and androgen dominance as the source. Accordingly, a dose of 0.5 mg of dexamethasone 4 times meant for four days is given every day, and an androgen panel along with cortisol levels will be considered after the final dose in the subsequent morning. The dominance of ACTH-dependent adrenal function by dexamethasone results in levels of plasma-free testosterone fall below 8 pg/ml, total testosterone below 35 ng/dl, DHEA sulfate below 80 µg/dl and plasma cortisol below 1.5 µg/dl [32,33].

1.3 Laboratory investigations

Serum AMH levels are used as investigatory parameter because the levels are 2-4 times more than normal in PCOS with the proposed value standing at 4.9 ng/ml using enzyme immunoassay (AMH-EIA). The advantage is that assessment is achievable at any stage during menses [12]. Pelvic examination through TVS is performed to scan ovaries cysts, exclude ovarian tumors, and endometrial hyperplasia changes [21]. The hormonal profile includes assessment of β-HCG to exclude oligomenorrhea; FSH, LH, PE2 to exclude amenorrhea, and premature ovarian failure; thyroid function tests to exclude hypothyroidism; prolactin to exclude hyperprolactinemia; androgens to exclude congenital adrenal hyperplasia or androgen secreting tumors and subsequently confirm PCOS [21,33]. Metabolic profiling includes OGTT to exclude type 2 DM; fasting lipid to exclude dyslipidemia; dexamethasone/cortisol levels to exclude Cushing's syndrome [21,33]. Despite the impact of PCOS on woman's health is out of the closet, the stigma associated with it, still, remains a neglected issue in the global response. Learning that they have PCOS, women feel shattered and emotionally, many express shame, anger, guilt, blame, denial and in such cases, considering fertility

treatment possess moral, ethical and religious dilemmas in their life. There is psychological wrenching through decreased self-confidence, sexual dissatisfaction, loss of feminine identity, imperfect body image, and avoidance of social interaction to name a few [24,25]. Hence, patient assessment is highly recommended to describe physical, psychological and social components of health status which is achieved through PCOS disease specific tools - PCOSQ, MPCOSQ and PCOSQ-50 [24].

2. Clinical significance

Recent studies have noted an estimated 4-times augmented peril for NAFLD among the PCOS population with underlying pathogenesis of complex interplay between androgen excess, insulin resistance, and obesity. NAFLD has a high mortality rate as it causes continuous inflammatory morphological changes, starting from hepatic steatosis, continuing to non-alcoholic steatohepatitis (NASH), and ending with stages of either hepatic cirrhosis, liver failure or hepatocellular carcinoma [34,35]. Insulin resistance with compensatory hyperinsulinemia affects about 70% PCOS population and is associated with a high prevalence of type 2 DM (79%) and central obesity (60%). Triglyceride levels more than 150 mg/dl, HDL levels less than 50 mg/dl, BP more than 130/80 mm Hg, OGTT level more than 100 mg/dl and Abdominal obesity more than 88 cm., with the presence of at least 3 findings is considered diagnostic of metabolic syndrome [34,35]. Chronic anovulation with hyperinsulinemia might induce aggravation of endometrial proliferation resulting an increased risk of endometrial and ovarian carcinomas [12].

3. Management

The goal is to resolve through non-pharmacological and pharmacological approaches.

3.1 Lifestyle modifications

Dietary Intervention in form of nutritionally adequate weight loss diet is proven to be beneficial, particularly, in improving insulin resistance and reducing excess androgen levels, and is regarded as first-line treatment [10,12]. Regular exercise leads to improvement in insulin sensitivity, SHBG and lipid levels and decreases in androgen levels, weight, and blood pressure, thus enhancing a healthy physique and mood and ameliorating anxiety and depression [12]. Medical Nutrition Therapy sheds light on Nutrition Diagnosis which screens for the presence of nutritional deficit development that needs to be addressed with immediate action, Nutrition Intervention that includes specific remedies which the patient is comfortable with, such as healthy meal – planning strategy, controlling food size portions etc., and Nutrition Monitoring through follow-ups for evaluating outcomes and modify interventions as required [12,36].

3.2 Appropriate drug therapy

Before prescribing treatment, it is necessary to obtain a complete history of the patient including – menstrual history, onset and progression of symptoms, weight changes, presence of hair loss and acne, and family history of similar complaints. Also, a thorough physical examination is conducted to establish the extent of symptoms, and signs of abnormalities – masculinization, virilization, thyroid enlargement and presence of any pelvic/abdominal mass [10,25].

For menstrual regularity, OCPs are considered primary intervention because these induce regular menses which is more beneficial than any other therapeutic result. Commonly used OCPs are estrogen – progestins that act by inhibiting ovarian function and suppressing free testosterone levels along with lowering DHEA sulfate and elevating levels of SHBG [32]. Progestin therapy includes medroxyprogesterone acetate (MPA) at dose of 5-10 mg/day for 10-14 days each month to treat amenorrhea or dysfunctional uterine bleeding by preventing atypical endometrium rise, however, there is no subdue of ovarian – androgen synthesis [15]. In cases of heavy DUB, Oestrogen can be prescribed with a dose of 1 tablet thrice daily for 7 days, with a gap of five days, and then continued.

These drugs are usually contraindicated in venous thrombosis cases and side effects include abdominal pain, mastalgia, heavy withdrawal bleeding, reduced libido, weight changes, confusion etc., [1]. Considering infertility management, Clomiphene Citrate is taken for resolving chronic anovulation with 50 mg/day for 5 days initially. If response not achieved after the first cycle, an increased amount of 100 mg is recommended, but after a gap of at least 30 days of previous therapy. In infertility management, usually, maximum six cycles of therapy can be attempted before any further assessment. Studies have proven that clomiphene drug induces an estimated 30% of successful pregnancies [4].

In hyperandrogenism reduction, therapeutic acne intervention is commonly through benzyl peroxide, clindamycin, retinoid creams etc., which are applied on affected skin areas. Although, patients with harsh acne consider antibiotics, mostly, tetracycline or oral isotretinoin management [12]. Hirsutism along with medications needs cosmetic amelioration to slow down hair growth which includes trimming, waxing, inhibition of hair development by eflornithine hydrochloride topical application, and dermal papilla annihilation by electrolysis or laser therapy, however, it has consequences like itchiness and tenderness on the skin surface [8,36]. For androgen suppression, the most popular are oral contraceptives (OCPs) which suppress LH and FSH levels causing a decrease in ovarian androgen production resulting in improvement of acne and hirsutism within three months [22,29].Most used is Yasmin comprising of ethinyl oestradiol (30µg) and drospirenone (3mg) and its mild anti-mineralocorticoid and anti - androgenic behavior makes this medication suitable to diminish hyperandrogenic effects [32]. Effects are observed after 9 months due to long growth cycles of sexual hair follicles. The most used anti-androgen is Spironolactone, 25-100 mg twice daily which lowers the hirsutism score by one-third and for its low cost, availability, high potency, and safety [32,36]. However, side-effects include vaginal/uterine bleeding, reduced libido, dysuria, etc., and contraindicated in adrenal, hepatic, or renal insufficiency cases [8].

Insulin resistance is resolved through, Metformin 500 mg thrice daily or Myoinositol 3g/day acts by reducing the sugar concentration in plasma and recuperating glucose with its necessary usage along with a decrease in the production of glucose in the liver, hence, essential for menstrual regularity, enhancing ovulation rate and pregnancy chances [1,12]. The above medications are effective in providing symptomatic relief, though, findings reported physical health to be affected due to adverse effects such as diarrhea (80%), trailed by sickness (66%), temperament disorders (64%), sore breast (60%), and back discomfort (43.6%) [1,31].

3.3 Surgical Measures

In such cases, pre-operative screening is done, and contraindications are excluded such as patient hemodynamically unstable, severe cardiopulmonary disease, significant hemoperitoneum, intestinal obstruction etc., Laparoscopic Ovarian Drilling is commonly preferred and achieved using mono/bipolar cautery or by laser through which cortex is usually punctured up to 3-5 mm depth at 4-6 sites [28,34]. A retrospective study by Yanamandra and Gundabattula among women who underwent laparoscopy and hysteroscopy followed by ovarian drilling was conducted in response to primary infertility treatment and reported an estimate of 50% enhanced conception [10].

Conclusion

Available studies suggest, PCOS is a complex heterogenous endocrinological syndrome seen in women, accompanying life-term morbid conditions. Prevalence in our country ranges from 3.7% - 22.5% and no constant treatment is present due to its multifaceted nature. Accurate diagnosis at a young age can be the key factor and physicians should be familiar with the PCOS phenotypes. The most preferred screening is plasma free testosterone level, while, ultrasonography helps in the differential diagnosis. The major clinical manifestations include chronic anovulation, menstrual irregularities and change in physical appearance such as obesity, acanthosis nigricans, hirsutism, and acne which adversely leads to the development risk of endometrial hyperplasia, infertility and

metabolic and psychological distress respectively. Insulin – lowering treatment, metformin, spironolactone, restoring ovulation using OCPs, progestins and antiandrogens and IVF in refractory scenarios to increase chances of successful pregnancy has been reported on ameliorating symptoms. Review analysis of women's health created an influence on the treatment success, hence, might add necessary information in clinical trials for evaluating the effectiveness of various treatment modalities and also, to the natural history studies. Young females counselling must be assessed for awareness so as to eliminate the stigma associated with it and to empower and support the PCOS women to take decisions for management and better health in present and future.

Conflicts of interest
The authors do not declare any conflict of interest.

Authors' contributions
All authors were involved in the conceptualization of the study. Deeksha Rana, Neema Acharya, Sandhya Pajai and Shazia Mohammad sourced all materials, data analysis and drafted the manuscript. Neema Acharya and Shazia Mohammad stated modifications in the draft to improve the content.All authors read and approved the final version of this manuscript.

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Tables and Figures

Table 1:Possible phenotypes in PCOS women according to Rotterdam Criteria.

Phenotype	**Hyperandrogenism**	**Anovulation**	**Polycystic Ovarian Morphology**
Type A (Classic)	✓	✓	✓
Type B (Classic Non – Cystic)	✓	✓	✓
Type C (Non – Classic Ovulatory)	✓		✓
Type D (Normoadrogenic)		✓	✓

Table 2: Research studies to reflect on clinical manifestations observed in PCOS women.

Study	**Year**	**Sample Size**	**Clinical Features**
Upadhye JJ et al	2017	200	6% reported PCOS. Among these, 33.5% acne,16.5% obese,16% irregular menses and 5% had hirsutism.16.5% consulted doctor, 9% did USG, and 1% opted ayurvedic and homeopathic treatment.
Sidra S et al	2019	440	59.8% reported PCOS. Among these, 63.2% had hyperglycaemia, 61.8% depression, 22.7% DM and 7% HTN. 85% had poor QoL.
Tabbassum et al	2020	100	All diagnosed PCOS. Among these 27% infertile.
Mehta AV et al	2021	600	12% diagnosed PCOS. Among these, 29% irregular menses and 25.78% obese.
Ramanand SJ et al	2021	120	All diagnosed PCOS. Among these, 31.4% high DHEA levels, 6.6% baldness, 44.1% AN and 5% hypothyroid.

Table 3: Diagnostic criteria to be considered for quick conclusion and medical intervention.

Parameters	**NIH CRITERIA (1990)**	**ASRM/ESHRE ROTTERDAM (2003)**	**AE-PCOS SOCIETY (2006)**
Ovulation	Chronic anovulation	Oligo/anovulation	Oligo/anovulation
Hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism
Ovarian Morphology	————	Polycystic ovarian morphology	Polycystic ovarian morphology
Number of criterions required for diagnosis	Both criteria required along with exclusion of other endocrinopathies.	At least two criteria required along with exclusion of other endocrinopathies.	Hyperandrogenism and one other criterion required along with exclusion of other endocrinopathies.
Exclusion of other endocrinopathies – Cushing syndrome, thyroid disease, androgen secreting tumours, drug induced androgen excess, hyperprolactinemia.			

Figure 1:Factors contributing towards the high prevalence of PCOS disorder in reproductive women.

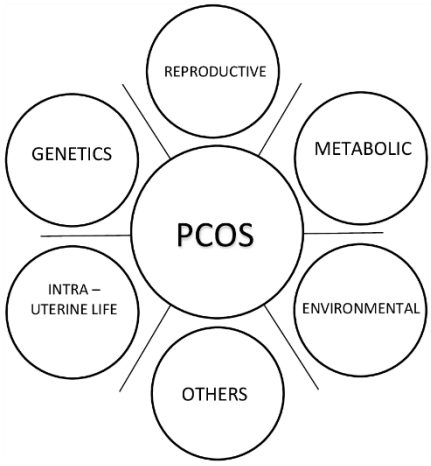

Figure 2: Depicted the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method in the present review.