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Review Article

AN UPDATED OVERVIEW OF POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal Syndrome, was first described in 1935. PCOS, which may also be referred to as polycystic ovary disease is the most common hormonal disorder found in premenopausal women. PCOS is the most common endocrine disorder in women of reproductive age and is the most common cause of infertility due to ovulation. A PCOS is an endocrine disorder which affects the adolescent girls. A PCOS is a condition in which a woman has an imbalance of female sex hormones. This may lead to changes in the menstrual cycle, cyst in the ovary, failure to conceive, and other health problems. It is a common health problem among teenagers and young women. It affects 5–10% of women in their reproductive years. These problems cause infertility. Two principal components to diagnose this syndrome are menstrual dysfunction and clinical or laboratory hyperandrogenism in which these items are used in clinical diagnosis. PCOS is a hormonal disorder that affects between 5% and 10% of women of reproductive age and remains the most enigmatic reproductive disorders. The most common symptoms of PCOS are obesity, acne, amenorrhea, irregular menstrual cycles, hirsutism, insulin resistance (IR), and high cholesterol. Due to the varied nature of PCOS and the large range of possible signs and symptoms, health personnel need a thorough knowledge of the disorder and its management. It is a major disorder characterized by elevated levels of male hormones (androgens), acne, and hirsutism. It can even cause IR, anovulation, and infertility on prolonging incidence of cysts. One of the treatments for PCOS is the use of synthetic medicine, which can help to treat PCOS but with side effects. However, many women who suffer from PCOS opt to use alternative medicine in conjunction with traditional medicine to improve their condition. There are some herbs that are very helpful in treating PCOS. Since PCOS is a curable disorder, it can be cured by the use of natural remedies or allopathic medication. There is a growing interest in herbal remedies or allopathic medication to cure the PCOS. There is a need to change the lifestyle management, diet to control the PCOS level. The natural remedies include treatment with phytoestrogenic and non-estrogenic herbs such as Licorice, Ginseng, Black cohosh, Dong, soy, evening primrose, honey, fenugreek, Schisandra root, and many other which are effective and safe. Many plants have been highly esteemed sources and have advantages which reduce PCOS and also having a hypoglycemic effect. In this review, an attempt has been made to study the use of natural remedy for the treatment of PCOS.

Keywords: Hirsutism, Polycystic ovary syndrome, Hyperandrogenism

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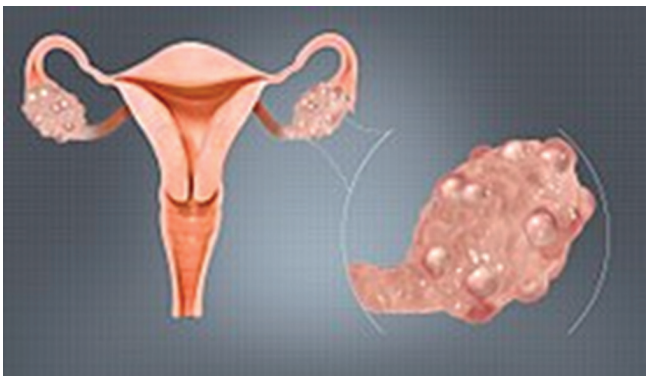
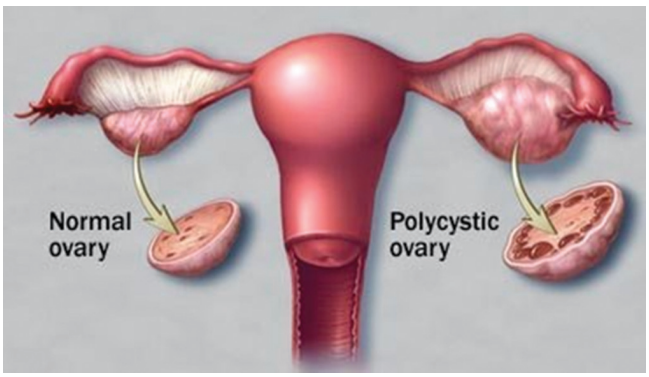
INTRODUCTION

Polycystic ovary syndrome (PCOS) is a set of symptoms due to elevated androgens (male hormones) in females. Signs and symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, and velvety skin. Associated conditions include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer [1].

PCOS is due to a combination of genetic and environmental factors. Risk factors include obesity, a lack of physical exercise, and a family history of someone with the condition. Diagnosis is based on two of the following three findings: No ovulation, high androgen levels, and ovarian cysts. Cysts may be detectable by ultrasound. Other conditions that produce similar symptoms include adrenal hyperplasia, hypothyroidism, and high blood levels of prolactin [2].

PCOS has no cure. Treatment may involve lifestyle changes, such as weight loss and exercise. Birth control pills may help with improving the regularity of periods, excess hair growth, and acne. Metformin and anti-androgens may also help. Other typical acne treatments and hair removal techniques may be used. Efforts to improve fertility include weight loss, clomiphene, or metformin. *In vitro* fertilization (IVF) is used by some in whom other measures are not effective. PCOS is the most common endocrine disorder among women between the ages of 18 and 44. It affects approximately 2–20% of this age group, depending on how it is defined. When someone is infertile due to lack of ovulation, PCOS is the most common cause. The earliest known description of what is now recognized as PCOS dates from 1721 in Italy [3].





The PCOS is one of the most common endocrine-reproductive metabolic

disorders of humans, affecting 5–15% of women worldwide, depending on the criteria used. The symptoms of PCOS include, somewhat variable, hyperandrogenism (HA), ovulatory dysfunction (OD), polycystic ovarian morphology (PCOM), gonadotropic abnormalities, and insulin resistance (IR), and compensatory hyperinsulinism. The disorder is considered to be a complex genetic trait with a high degree of heritability. Although there are different criteria for defining the disorder, more important is the need to clearly define the phenotype of the patient being considered. PCOS phenotypes can generally be categorized, in their simplest forms, into four types: (a) Phenotype A, demonstrating evidence of HA, either clinical, such as hirsutism, and/or biochemical, i.e., hyperandrogenemia, OD, often reflected by menstrual dysfunction, and PCOM; (b) phenotype B, which includes HA and OD, but not PCOM; (c) phenotype C, including HA and PCOM, but not OD; and (d) phenotype D, with OD and PCOM, but not HA. Metabolically, phenotypes A and B (also called "classic PCOS") behave similarly, with approximately 75–85% demonstrating IR and some form of metabolic dysfunction. These individuals have an increased risk of glucose intolerance and diabetes. Alternatively, PCOS women with phenotype D (also called "nonhyperandrogenic PCOS"), who do not demonstrate overt evidence of androgen excess, have little evidence of metabolic dysfunction and are at low risk of developing disorders of glucose intolerance. Patients with phenotype C (often referred to as "ovulatory PCOS") have levels of metabolic dysfunction and risk that are somewhat less than those with the classic forms of PCOS but still measurably higher than those of control subjects or nonhyperandrogenic PCOS women. Reproductively, women with OD will obviously demonstrate greater degrees of subfertility than will ovulatory PCOS patients [4].

PCOS women with PCOM, which are actually the vast majority of patients with the disorder (although PCOM is also present in a significant fraction of non-PCOS individuals), are at greater risk of ovarian hyperstimulation if treated with ovulation induction for their infertility. Although the heritability of PCOS appears to be high, we should note that the proportion of heritability accounted for by the PCOS loci identified so far by current large-scale genome-wide association studies is <10%, which is not different from that observed with other complex genetic traits. In addition, and not reviewed in the present Views and Reviews series, we are also beginning to discover that epigenetic variations, including gene and histone methylation, and the action of histones, micro RNAs, RNA binding proteins, among others, also appear to play a role in determining the PCOS phenotype (1–5). Environmental determinants of PCOS and its phenotype are less well studied. Although we understand that obesity (and associated increased sedentary lifestyle, poor nutrition, and overeating) plays a role in worsening the metabolic complications of PCOS, there are limited data to suggest that obesity itself drives the development of the disorder, or is there clear evidence of significant differences in diet between women with and without PCOS. Other environmental factors determining the prevalence or phenotype of PCOS may include environmental toxins and socioeconomic status. We know even less regarding the role that geography, such as proximity to large bodies of water, altitude, latitude/longitude, climate, or terrain, play in determining the prevalence or presentation of PCOS. On cursory consideration, PCOS appears to represent an evolutionary paradox. That is, it is a disorder associated with reproductive dysfunction (reduced reproductive fitness), but that appears to have persisted, and even thrived, for millennia. A better understanding of the evolutionary determinants of PCOS potentially allows us to better identify the fundamental intrinsic aspects of the disorder [5].

Brief introduction to evolutionary biology and argue that from an evolutionary perspective, the pathogenic mechanisms underlying PCOS might be candidate factors for survival advantage. There is limited evidence for positive selection in PCOS and that more likely the evolution of PCOS is the result of nonadaptive mechanisms, including genetic drift and population balance, due to sexual antagonism. Better understanding and defining the determinants underlying the prevalence, global distribution, and phenotype of PCOS has the potential to guide the search for molecular and genetic targets for the disorder and to develop interventions to predict, prevent, and treat the disorder [6].

PCOS is the most common cause of chorionic anovulation and anovulatory infertility. PCOS is mentioned as a common endocrinopathy in women who are at reproductive age, and it is associated with metabolic disorder and reproductive dysfunction. Ovarian dysfunction continues to be the main feature, which makes this syndrome the major cause of anovulatory associated with infertility. Most say 5–10% of reproductive-age women are affected, but some say 6.6–8% and some others say PCOS is a disorder affecting up to 6–10% of women in reproductive age. This syndrome can be defined by specific clinical and biochemical criteria and also using ultrasonography. Clinical manifestations of PCO include menstrual irregularities, signs of androgen excess, obesity, and sometimes hirsutism. Hirsutism is defined as a score of eight or more on the modified Ferriman-Gallwey index. Oligomenorrhea is also one of the clinical manifestations of PCOS. Oligo/amenorrhea cycles are defined as eight or less cycles per year, and biochemical androgen measurements should be fulfilled in the follicular phase in patients with preserved menstrual cycles. The clinical manifestations of PCOS are heterogeneous, and it looks possible that patients may present some of the various symptoms and signs. The heterogeneity seems to be adjusted by several factors, such as genetic factors, nutritional condition in the uterus, prenatal androgen exposure, IR, exaggerated adrenarche, and body weight changes [7]. Environmental status and factors, such as obesity, appear to exacerbate the underlying genetic predisposition. PCOS is characterized by increased levels of circulating androgen, PCOM, arrested follicle development, and anovulatory infertility.

PCOS is commonly associated with IR, hyperinsulinemia, components of the metabolic syndrome (MetS), and oligo anovulatory cycles. Although some of the clinical symptoms and presentations of PCOS is dependent on age, ovarian failure and hyperandrogenism (HA) are common characteristics at any age.

Although the pathogenesis of PCO syndrome is unknown, it is believed that PCO is the result of different interactions between genetic and multiple environmental factors. This syndrome is a multi-factorial disease, and the different susceptibility of patients is probably determined by several genetic and environmental risk factors as told above.

While during childhood, first signs of the syndrome can be perceptible, the unique features of PCOS in puberty are not yet clear. Despite all of these difficulties, PCOS early diagnosis has great and undeniable importance, because its presence is related to a greater risk of future infertility, a disease which is related to the cardiovascular system, diabetes mellitus (DM) (type II), and MetS. The PCOS diagnosis in puberty can be difficult, because anovulation is common in young girls (in the first 2 years of menarche half of the menstrual cycles are anovulatory), and multiple follicles display on ultrasound is also a fairly common finding during puberty. Thus, the main findings at present which indicate a diagnosis of the syndrome at this age are biochemical HA or clinical HA with hair excess [8].

PCOS is a disease that often presents during adolescent, but there is an overlap between features of PCOS and physiological findings observed during the normal progression of puberty, and this matter makes the diagnosis more complicated in this age group. Further, the absence of universally accepted criteria for PCOS diagnosis for adolescents causes not to have a diagnosis with certainty, and the variable diagnosis of PCOS poses a vast range of challenges. Different criteria that used for diagnosis of syndrome can result in different prevalence PCOS.

Prevalence of the syndrome varies according to diagnostic consensus used, with estimates ranging from 9% according to the National Institutes of Health consensus, up to 18% with the Rotterdam consensus. It is obvious that early diagnosis in adolescent age group

would allow us for earlier treatment and even prevention of PCO-associated morbidity, but it should be noticed that premature diagnosis carries risks of psychological distress and unnecessary treatment.

Numerous surveys have studied about the appropriateness of applying adult criteria for adolescents because the sign of PCOS during the post-pubertal period overlap with normal physiologic changes in puberty. A high rate of menstrual and anovulatory cycles could be observable in this age group, as well as difficulties that may occur in interpreting evidence of HA, either clinical or biochemical. A very common complaint is acne during adolescence, but alopecia is one of the rare phenomena in girls, and sometimes hirsutism is borderline and aggravates slowly. Thus, several criteria have been suggested specifically for adolescent [9].

The adolescent period is a unique period where there is a change from childhood to adulthood, a time of physiological, psychological, social, and emotional adaptation. During this period, individual attains physical and sexual maturity, whereas emotional maturity will be imbalanced. The changes in the adolescent period have important implications to understand the health risks associated with this syndrome. During this period, the body changes and there will be the development of secondary sex characteristics. Any difference in secondary sex characteristics can inversely affect the physical and emotional adaptation of the adolescent.

PCOS is a condition in which woman has an imbalance of female sex hormones. This may lead to changes in the menstrual cycle, cyst in the ovary, failure to conceive, and other health problems. It is a common health problem among teenagers and young women. It affects 5–10% of women in their reproductive years. These problems cause infertility. Although there is no cure for PCOS, there are several ways to treat and manage the condition. If a girl is overweight, weight loss can be very effective in lessening many of the health conditions associated with PCOS. Sometimes weight loss alone can restore hormone level to normal, causes many of the symptoms to disappear or become less severe. Healthy food habits and exercise helps to combat weight gain. Research has suggested that PCOS may be related to increased insulin production. PCOS seems to run in families, too, so if someone in the family has it, they might be more likely to develop it. India has witnessed about 30% rise in PCOS cases in the last couple of years. Lack of knowledge and lifestyle changes are considered to be the major factor leading to this phenomenon. There is a need to increase awareness among women so as to avoid major cases of fertility problems in the future. A nurse holds a critical role in health care that goes beyond the day to day duties. Nurses are in a position to provide comprehensive care to adolescent afflicted with the syndrome. Essential elements of nursing practice should be included in nursing education. Hence, upgrading the knowledge regarding PCOS to nursing students will enhance the adolescent girls to modify their lifestyle and reduce the risk [10].

PCOS has been defined by the National Institute of Health and Rotterdam criteria as a hormonal disorder characterized by the presence of at least one polycystic ovary (presence of multiple cysts) accompanied by OD and excessive secretion of androgens. Consensus on women health aspect of PCOS has suggested different criteria for the diagnosis of PCOS in adolescents from those used for adults. According to its suggestions, PCOS in adolescent should include all the three elements of Rotterdam criteria in which oligomenorrhea should be present after 2 years of menarche or primary amenorrhea at the age 16 years; polycystic ovaries on ultrasound along with ovarian size of more than 10 cm^3 and hyperandrogenemia should be present. The occurrence of PCOS has been associated with an increased risk for type-2 diabetes, gestational diabetes, hypertension, and gynecological cancers. Studies have reported 10 times greater risk of developing type-2 diabetes in women affected by PCOS. The worldwide prevalence of PCOS ranges from 2.2% to 26%. The rates of PCOS have been reportedly high among Indian women compared to their Caucasian counterparts, with an estimated prevalence of 9.13% in Indian adolescents [11].

Clinical presentations of PCOS include abnormal facial and skin hair growth (hirsutism), acne, and irregular, or absence of, and menstrual periods. However, acne is most common during the adolescent phase of life and there is limited literature on adolescent androgenic alopecia. Differential diagnosis of PCOS includes congenital adrenal hyperplasia (late onset) hyperthecosis, Cushing syndrome, hyperprolactinemia, hypothyroidism, and ovarian and adrenal androgen-secreting tumors. Different categories in the clinical presentations of PCOS have been distinguished according to the Rotterdam criteria. They include:

1. "Classic PCOS" characterized by the presence or absence of ovarian cysts with excessive androgen secretion and irregular menstrual periods
2. "Ovulatory PCOS" characterized by the presence of increased androgen secretion and multiple cysts, and
3. "Non-androgenic PCOS" associated with irregular menstruation and multiple cysts.

The determinants of PCOS have been linked to both hereditary and environmental factors. The attributed hereditary factors include early age of sexual maturation, premature fetal development, and family history of PCOS among first-degree relatives. Studies have reported an earlier age at diagnosis of PCOS (9–12 years) among adolescent females with earlier maturation of sexual characteristics compared to their later counterparts (13–18 years). This has been attributed to an increased androgen secretion associated with early onset of puberty. It has been reported that premature fetal development leads to an earlier and more rapid onset of puberty with an increased risk of developing PCOS. Clinical manifestations of associated symptoms such as hyperinsulinemia have also been observed in the offspring of PCOS affected women long before the onset of puberty affirming the role of family history [12].

The associated environmental factors reported include physical inactivity, obesity, and its associated IR. IR which is of high prevalence in the Indian population has been consistently reported as a strong determining factor for the occurrence of PCOS in Indian adults and adolescents. While several studies have reported an association between excessive androgen secretion and the occurrence of IR in affected women, temporality has not been established. There are marked variations in the prevalence of IR across different geographical regions of India and among urban and rural settings. A higher prevalence of IR has been observed in urban Indian populations compared to their rural counterparts. This is suggestive that a marked difference could exist in the prevalence of PCOS among different settings [13].

Since the clinical manifestations of PCOS have been consistently observed in early adolescence, the increased risk of developing type 2 diabetes and its associated comorbidities during later years can be controlled by identifying high-risk populations and implementing preventive measures. However, the nature of the environmental and lifestyle determinants of PCOS including physical activity and obesity is suggestive of the fact that variations could exist in the prevalence of PCOS in urban and rural settings due to dissimilar dietary practices and the level of physical activity. Although studies have reported the prevalence of PCOS in Indian adolescents, no studies have examined the differences in prevalence rates in urban and rural settings. We hypothesize that the burden of PCOS will be considerably lower among rural Indian adolescents compared to their urban counterparts. Such results could foster the implementation of lifestyle preventive measures for PCOS and its associated comorbidities in different settings at an earlier stage. The aim of this study was to determine urban-rural differences in the burden of PCOS among Indian adolescent females aged 12–19 years.

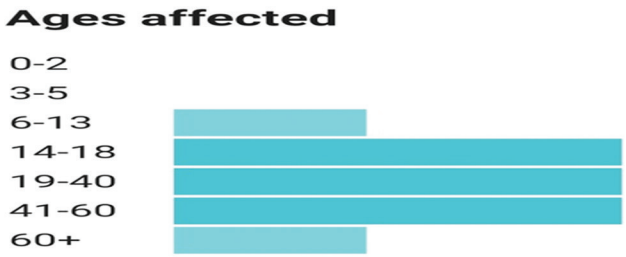
PCOS is one of the most common reproductive endocrinological disorders with a broad spectrum of clinical manifestations affecting about 6–8% of women of reproductive years. The diverse manifestations of PCOS start at an early age when a girl is maturing into a young woman. During this pubertal transition, several features

may be in evolution and thus many findings may be transitory which stabilize later during adolescence. However, it is important to make an early diagnosis to prevent early and late sequel of the syndrome. PCOS a diagnosis of exclusion has been a topic of debate, and many consensus definitions have evolved over time. The National Institute for Health (NIH) Criteria 1990 were revised in 2003 and Rotterdam criteria have been adopted world over. However, recently in 2006, Androgen Excess Society (AES) has come up with a consensus statement, defining PCOS as a hyperandrogenic state and emphasizes the presence of either clinical and/or biochemical features of HA along with other features of PCOS for diagnosis.

Globally, prevalence estimates of PCOS are highly variable, ranging from 2.2% to as high as 26%. Community-based studies using Rotterdam criteria among reproductive age group women have demonstrated varied prevalence figures in few Asian countries ranging from 2% to 7.5% in China to 6.3% in Sri Lanka. Studies among several Caucasian populations using NIH criteria reported PCOS in the range of 5–8%. An Australian retrospective birth cohort study of 728 women reported a prevalence of 11.9±2.4% as per Rotterdam criteria, which increased to 17.8±2.8% when imputed data were included. Under the AES recommendations, PCOS prevalence was 10.2±2.2% and 12.0±2.4% with the imputed data. Although there are limited studies of PCOS in India, the observational studies by endocrinologists, gynecologists, and dermatologists relate to diverse aspects of PCOS. Prevalence of obesity and DM in most industrialized countries, including India is also on the rise due to urbanization and change in lifestyle. Most of the young population does not visit health facilities until they have a late sequel of the problem. Most prevalence studies in India are in hospital set-ups, and recently, a few studies among adolescents in schools report the prevalence of PCOS as 9.13%–36%. It is appropriately pointed by Gainie and Kalra that the health budget of India is unlikely to meet the costs posed to tackling the associated multiple consequences of PCOS. It is time that this warning is heeded and at the national level, the disease is recognized as an important non-communicable disease. Studies have demonstrated that the cost of diagnostic evaluation accounts only for a relatively minor part of the total costs of managing PCOS (approximately 2%). Hence, more widespread and liberal screening for the disorder appear to be a cost-effective strategy, benefiting earlier diagnosis and intervention and possibly the amelioration and prevention of serious sequel. The varying prevalence of PCOS, in general, is mainly due to using different diagnostic criteria, the heterogeneous presentation of symptoms, logistic difficulty to carry out blood or ultrasound tests, and the varied age groups and ethnic populations that have been studied [14].

This has resulted in prevalence studies being based on convenience samples such as university employees or blood donors without any representativeness of these subgroups. With this background, a community-based study was undertaken in Mumbai, India, to screen adolescents and young unmarried girls aged 15–24 years for PCOS.

PCOS is thought to be the most common endocrine disorder found in women. PCOS has a variety of phenotypes; therefore, it presents a broad spectrum of clinical symptoms and risk factors. Common symptoms include irregular menstrual cycles, ovarian cysts, and hirsutism. PCOS impacts women of all races and ethnicities who are of childbearing age. PCOS is associated with a significant increase in risk factors such as cardiovascular disease (CVD), type-2 diabetes, and infertility. The etiology of PCOS is not completely understood, although genetic and lifestyle factors are known to influence the etiology and IR plays a key role in the pathogenesis of PCOS. IR is thought to play a central role in the etiology of PCOS and is present in 50–90% of women with PCOS (depending on diagnostic criteria used), which is significantly worse than age- and body mass index (BMI)-matched control women. Data estimate that 38–88% of women with PCOS are overweight or obese across the world, with an increased rate in the United States to mirror the higher obesity rates in the non-PCOS population. IR does present in individuals with lean PCOS, as well as overweight and obese women. Common treatments for IR include Metformin and weight reduction/lifestyle interventions. Another characteristic feature of PCOS is HA, which refers to elevated male hormones (androgens), such as testosterone. Hyperandrogenemia can be diagnosed clinically through the presence of Acne, Hirsutism (unwanted hair growth around the face, chest, or trunk), or Alopecia (male-pattern baldness or the thinning of hair). It can also be diagnosed biochemically through a blood test. In a large study of over 1000 women with androgen excess, 659 presented with hirsutism and 78.4% of the hirsute women were diagnosed with PCOS under the 1990 NIH criteria. Common treatment of hyperandrogenic symptoms includes spironolactone or finasteride. PCOS is often associated with infertility, which is present in an estimated 40% of women diagnosed with PCOS. The root of infertility in these women is likely from reoccurring menstrual disturbances, which is often presented as oligomenorrhea (with 85–90% of women with PCOS), amenorrhea (present in 30–40% of women with PCOS), or abnormally long or erratic menstrual patterns. It is also important to mention that up to 30% of women diagnosed with PCOS have normal menstrual cycles, which emphasizes the high degree of heterogeneity in this condition. Mental health outcomes are also a concern when examining a multifaceted condition with dermatological symptoms, weight gain, fertility issues, as well as a variety of risk factors. A cross-sectional, multi-centric study in Iran on 100 women with PCOS and found that 45% presented with depression and 30% were considered for possible cases of other mental disorders. Another study in the UK found that PCOS had a negative impact on health-related quality of life, even when compared with a variety of other health conditions with a relatively small sample size using a reliable and valid evaluation tool [15].



Pathophysiology

Despite being one of the most common endocrinopathies, a comprehensive explanation of pathophysiology is still lacking. The heterogeneity of PCOS may well reflect multiple pathophysiological mechanisms, but the definition of each contributing mechanism has been slow to emerge. Conventionally, it has been useful to consider the PCOS as the result of a "vicious cycle," which can be initiated at any one of many entry points. Altered function at any point in the cycle leads to the same result: Ovarian androgen excess and anovulation. Several theories have been proposed to explain the pathogenesis of PCOS:

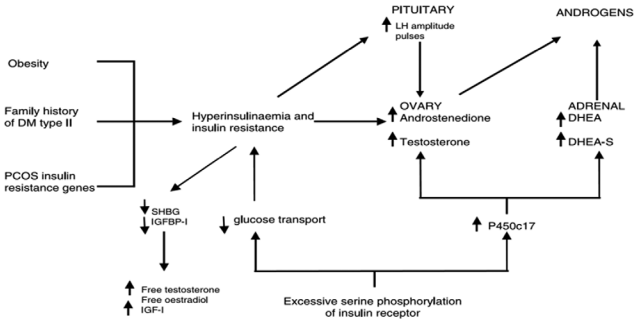
1. A unique defect in insulin action and secretion that leads to hyperinsulinemia and IR.
2. A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude.
3. A defect of androgen synthesis that results in enhanced ovarian androgen production.
4. An alteration in cortisol metabolism resulting in enhanced adrenal androgen production.

It must be accepted, however, that each of these is artificial stating points to our understanding of the metabolic–ovarian–pituitary circuitry being closely interrelated.

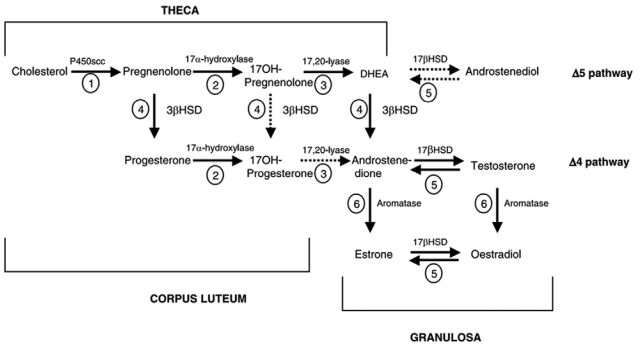
IR

The first recognition of an association between glucose intolerance and HA was made by Achard and Thiers (1921) and was called the

diabetes of bearded women. The association between increased IR and PCOS is now well recognized. IR is defined as a reduced glucose response to a given amount of insulin. There are several mechanisms contributing to the state of IR: Peripheral target tissue resistance, decreased hepatic clearance, or increased pancreatic sensitivity. Studies with the euglycemic clamp technique indicate that IR is a common feature of the syndrome, and both obese and non-obese women with the syndrome are more insulin-resistant and hyperinsulinemic than age- and weight-matched normal women. However, obese PCOS women had significantly decreased insulin sensitivity compared with non-obese PCOS women (Dunaif, 1995). For example, reduced insulin sensitivity in lean PCOS compared with lean controls, a further decrease in obese controls and a two-fold further reduction in obese PCOS, suggesting that obesity is additive to IR related to PCOS. Consistent with the degree of IR, the manifestation of compensatory hyperinsulinemia in lean PCOS women was incipient, being evident only in response to meals [16]. Collectively, these observations indicate that IR is a common finding in women with PCOS independent of obesity and that IR in obese PCOS is composed of dual contributions, one unique to PCOS and the other obesity-specific. Not all studies, however, have shown IR in lean PCOS subjects. Reports using an intravenous glucose tolerance test, a continuous glucose infusion model or a hyperinsulinemic euglycemic clamp found normal insulin action in normal weight PCOS patients. There are several possible reasons for these discrepancies which any case common in PCOS research papers. The composition of study groups varies depending on local diagnostic criteria; there is no standard definition and assessment of IR; ethnic variations in central adiposity, insulin sensitivity, and the prevalence of a positive family history of type-2 diabetes are rarely taken into account; many studies with small numbers of subjects may contain type-2 statistical errors. In addition to decreased insulin sensitivity, pancreatic β-cell secretory dysfunction has been reported in PCOS. The β-cell defect – increased secretion of insulin under basal conditions and decreased secretion after meals – results in insufficient insulin secretion to compensate for the degree of IR. The decreased post-prandial secretory responses in these patients resemble the β-cell dysfunction of type-2 DM and are much more pronounced in PCOS women who have a first-degree relative with type-2 DM, suggesting an increased risk for developing glucose intolerance. Weight loss results in significantly improved IR, but the β-cell defect remains, suggesting that it may be the primary abnormality in PCOS. However, it showed that polycystic ovaries, unlike type-2 DM were not associated with a defect in the secretion of insulin. Finally, a reduction in the insulin clearance rate due to decreased hepatic insulin extraction has been reported to be partially responsible for the elevations in insulin concentration by some investigators. Several groups have a focus on mechanisms of insulin signaling to define the pathogenesis of IR in PCOS. Insulin action is mediated through a protein tyrosine kinase receptor. Tyrosine autophosphorylation increases the insulin receptor's tyrosine kinase activity, whereas serine phosphorylation inhibits it. The tyrosine-phosphorylated insulin receptor phosphorylates intracellular substrates, such as insulin receptor substrate (IRS)-1 and IRS-2 initiating signal transduction and the pleiotropic actions of insulin. A potential mechanism for IR in at least 50% of PCOS women appears to be related to excessive serine phosphorylation of the insulin receptor. A factor extrinsic to the insulin receptor, presumably a serine/threonine kinase, causes serine phosphorylation of the insulin receptor, leading to inhibition of signaling. It is believed that the defect in insulin action is limited to glucose metabolism, whereas other biologic actions of insulin – including those involved in steroidogenesis – are not impaired. Interestingly, serine phosphorylation of IRS-1 appears to be the mechanism of tumor necrosis factor-α-mediated IR of obesity. Serine phosphorylation also appears to modulate the activity of the key regulatory enzyme of androgen biosynthesis, P450c17, present in both the adrenal and ovarian steroidogenic tissue. Thus, serine phosphorylation has been shown to increase enzyme activity and androgen synthesis (Zhang *et al.*, 1995). Hyperandrogenism Several studies have demonstrated a positive correlation between fasting insulin levels and androgen levels. Furthermore, the severity of hyperinsulinemia correlates with the degree of clinical expression of the syndrome.



[Pathways leading to androgen excess in PCOS]



[Ovarian steroid biosynthesis]

Whether HA results from the hyperinsulinemia of IR, or vice versa, have been debated since this correlation was demonstrated. Most of the evidence supports hyperinsulinemia as the primary factor, especially the experiments in which decreasing the hyperandrogenemia by bilateral oophorectomy or the administration of a gonadotropin-releasing hormone (GnRH)-agonist has not demonstrated changes in the hyperinsulinemic state in PCOS and has also reported that antiandrogen therapy did not alter insulin sensitivity in PCOS. It is possible, however, that androgens may contribute to some extent to the associated IR of PCOS, as some investigators have found that IR was partially reversed during androgen suppression. In summary, these findings indicate that endogenous androgens do not play a central pathophysiologic role in sustaining IR in women with PCOS and that disordered insulin action precedes the increase in androgens. It is generally accepted that hyperinsulinemia augments androgen production in PCOS. Insulin may act:

- Directly, as a gonadotropin augmenting LH activity through stimulation of ovarian receptors of insulin and insulin-like growth factors (IGF);
- Indirectly, by enhancing the amplitude of serum LH pulses. Despite evidence that insulin promotes ovarian androgen production in PCOS, the exact mechanism on cellular level remains unclear [17].

Initially, insulin cross-reaction with the IGF-I receptor – similar in structure to insulin receptor – on the ovarian thecal cells was proposed as a possible mechanism of insulin-mediated HA. In view of the known actions of IGF-I in augmenting the thecal androgen response to LH, activation of IGF-I receptors by insulin would lead to increased androgen production in thecal cells. However, insulin has been shown to bind the IGF-I receptor with an affinity of 50–500 times lower than that of IGF-I. The crossover effect of insulin with the type-I IGF receptor, therefore, is an important consideration at high insulin concentrations. The existence of hybrid and atypical insulin/IGF-I receptors – which consist of a combination of α- and β-subunits of both receptors – has also been described. It is believed that these receptors can bind insulin and IGF-I with similar affinity. Furthermore, it has been proposed that insulin has specific actions on

steroidogenesis acting through its receptor, a pathway supported by *in vitro* studies of both granulosa. Interestingly, using anti-insulin receptor and antitype-I IGF receptor antibodies, not only demonstrated that insulin effects on human granulosa cell steroidogenesis *in vitro* must be mediated though its receptor but also excluded both the insulin/type-I IGF hybrid receptor and the type-I IGF receptor as possible insulin action-mediated receptors. Preliminary studies suggest that insulin enhances the amplitude of LH pulses but not their frequency in obese women with PCOS. This is consistent with the previous report that there is a general concordance of the diurnal pattern of LH levels and that of insulin levels in these women. Studies in which insulin levels have been suppressed by insulin-lowering agents suggest that insulin might also contribute to changes in ovarian androgen secretion through effects at the pituitary level. An alternative possibility is that the reduced secretion of LH with these therapies could be secondary to high progesterone levels following ovulation. Finally, insulin receptors have been identified in human pituitary tissue and insulin found to stimulate gonadotropin release *in vitro*, at least in rats proposed an insulin-mediated increase of ovarian cytochrome P450c17a activity, as an additional mechanism of insulin action in a subgroup of obese PCOS women [18].

Although each cell type of the ovary possesses the complete enzymatic complement required for steroid hormone synthesis, the predominant hormones formed differ among cell types. In the ovarian follicle, the Δ5-pathway is preferred for the formation of androgens and estrogens, because theca cells of human ovary metabolize 17-OH pregnenolone more efficiently than 17-OHP. The main pathway of steroid synthesis in human corpus luteum is the Δ4-pathway, which involves the conversion of pregnenolone to progesterone. The names of each enzyme are shown by each reaction: (1) P450scc, mitochondrial cholesterol side-chain cleavage enzyme, mediates 20α hydroxylation, 22 hydroxylation, and scission of the C20-22 bond, (2 and 3) P450c17 in the endoplasmic reticulum mediates both 17α-hydroxylation and scission of the C17, 20 bond, and (4) 3βHSD, a non-P450 enzyme bound to the endoplasmic reticulum, mediates both 3β-hydroxysteroid dehydrogenase and Δ5–Δ4 isomerase activities. The type II isoform is expressed both in gonads and adrenal glands. (5) 17βHSD, a non-P450 enzyme of the endoplasmic reticulum, converts estrone to oestradiol, androstenedione to testosterone, and DHEA to androstenediol, and vice versa. Nine human 17βHSD isoforms have been cloned and characterized to date. (6) P450arom in the endoplasmic reticulum mediates aromatization of the A ring of the steroid nucleus. The factors that determine which steroid is secreted by each cell type include the levels of gonodotropin and gonodotropin receptors, the expression of steroidogenic enzymes, and the availability of low-density lipoprotein (LDL) cholesterol [19].

In this study, a decrease in serum insulin concentrations with metformin, followed by a reduction of ovarian P450c17a activity, as demonstrated by a substantial reduction in the response of serum 17α-hydroxyprogesterone to the administration of leuprolide. An analogous report by that hyperinsulinemia may stimulate cytochrome P450c17a activity in another steroidogenic tissue of women with PCOS – the adrenal gland – further supports this hypothesis. There are two other important actions of insulin which contribute to HA in PCOS: The inhibition of hepatic synthesis of serum sex hormone-binding globulin (SHBG), which allows more free androgen and estrogen to be bioavailable, and the inhibition of hepatic production of IGF binding protein-1, which allows an increase in circulating levels of IGF-I and greater local activity. This is now known to be the mechanism for the frequently observed inverse correlation between peripheral insulin and SHBG levels. This relationship is so strong that SHBG concentrations are good markers for hyperinsulinemic IR, and reduced SHBG concentration is a predictor for the development of type-2 DM. The clinical implication of these findings is that amelioration of HA in women with PCOS may be achieved by interventions that improve insulin sensitivity and reduce circulating insulin levels. Indeed, weight loss in women with PCOS improves the endocrine and ovarian dysfunction, while the pharmacological approach with agents that either decrease insulin secretion, like diazoxide, or that improve insulin sensitivity, like metformin, or troglitazone has demonstrated conclusively that a reduction in serum insulin levels is associated with a reduction of ovarian androgen secretion in PCOS. The improvement of serum androgen levels with different drug classes, with a different mechanism of action, suggests an effect mediated by a reduction in circulating insulin levels, although a direct ovarian effect especially of the insulin-sensitizing agents cannot be excluded. These changes were independent of changes in body weight, although for metformin there still exists some controversy. The insulin-sensitizing agents, metformin and troglitazone, not only reduce circulating insulin concentrations but also reverse the metabolic and endocrine anomalies (decreased androgens, increased SHBG, decreased plasminogen activator inhibitor-1 consistent with improved fibrinolytic capacity, and decreased LH), and more recently, restoring menstrual abnormalities and improving the reproductive outcome in anovulatory PCOS women [20].

CVD

IR is considered to be a risk factor for coronary heart disease as it is associated with impaired glucose tolerance and type-2 DM, hypertension, abdominal obesity, and adverse lipid profiles **(**Orchard *et al.*, 1983), all features of the so-called "MetS X." Retrospective studies suggest that there is an association between PCOS and CVD. Arterial lesions were seen in 52 women and these women were more likely to report hirsutism, DM, hypertension, and previous coronary artery disease. Studies carried out a pelvic ultrasound scan for polycystic ovary morphology on 143 women undergoing cardiac catheterization. They reported no significant difference in the prevalence of polycystic ovaries in women with coronary artery lesions and normal arteries. However, women with PCOS had more affected segments. These studies suggest that there may be some association between PCOS and coronary artery disease risk. However, the studies are retrospective, contain a mixed group of pre- and post-menopausal women, are not controlled for obesity, and do not have rigorous criteria for the PCOS. They measured carotid artery intimal thickness by ultrasound in women with PCOS. The carotid artery intima-media thickness was significantly increased in women with PCOS, but there was no significant difference in the number of women with atherosclerotic plaques. Hemodynamic changes have also been reported in women with PCOS. In two consecutive studies, Prelevic reported lower cardiac flow velocity, higher resting forearm flow during reactive hyperemia, and lower incremental forearm flow in PCOS than in age-matched control women. In a subsequent study, Lees *et al.* (1998) reported a constrictor response to transdermal glyceryl trinitrate – a potent vasodilator which acts through the endothelial nitric oxide system – on uterine artery Doppler velocimetry in women with PCOS. A paradoxical constrictor response to 5% carbon dioxide, acting as a cerebral vasodilator, in the internal carotid artery in women with PCOS compared with women with normal ovaries. More recently, Paradisi *et al.* (2001) showed a positive correlation between abnormal endothelial function and testosterone levels in hyperandrogenic insulin-resistant women with PCOS, an association which was stronger than that of insulin sensitivity. All of these findings probably represent an abnormality in endothelial function in women with PCOS and are indicative of widespread changes in cardiovascular function in these women.

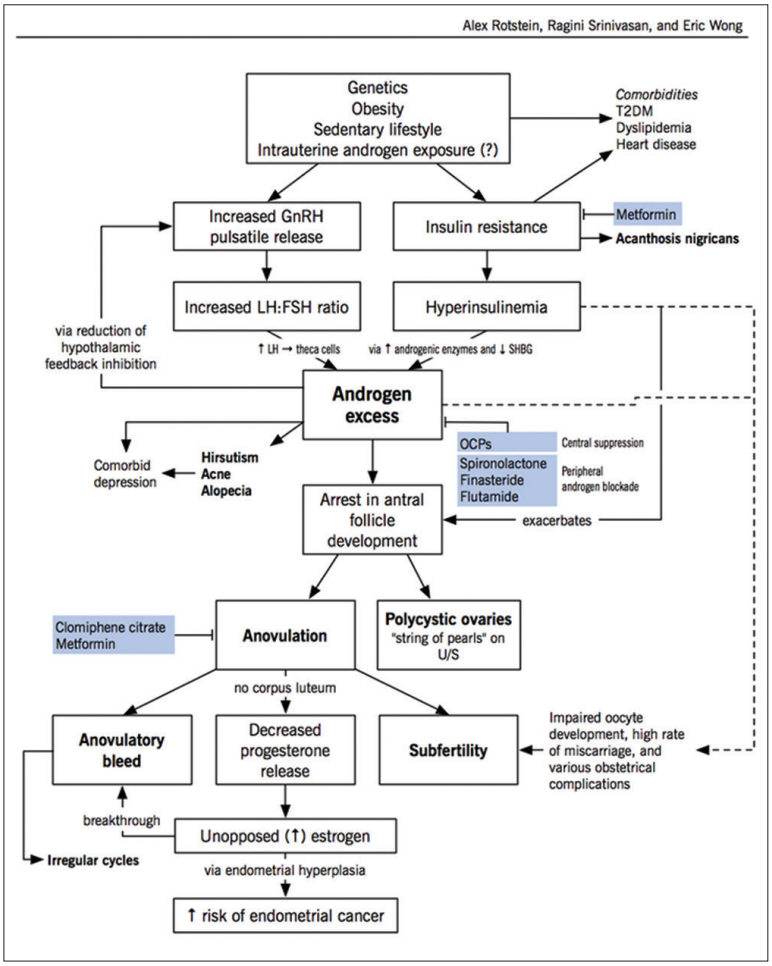
Neuroendocrine defect

LH hypersecretion – both basally and in response to GnRH administration – is a characteristic hallmark of PCOS. This phenomenon has been considered to be the primary abnormality in classic PCOS and thus, the cause of androgen excess. It is believed that the elevated LH levels are partly due to an increased sensitivity of the pituitary to GnRH stimulation, manifested by an increase in LH pulse amplitude and frequency, but mainly amplitude. The gonadotrophin pattern (high LH and low to normal follicle-stimulating hormone [FSH]) can also be due to the increased pulse frequency of GnRH secretion, attributed to a reduction in hypothalamic opioid inhibition due to the chronic absence of progesterone. It is likely that this increased activity is taking place at both hypothalamic and pituitary sites. Taken together, these data suggest that the increased plasma LH and GnRH/LH pulsatile secretion in PCOS are not simply a consequence of the low levels of progesterone due to anovulation, but reflect an underlying insensitivity of the hypothalamic

GnRH pulse generator to estrogen/progesterone inhibition. Finally, it was suggested that such insensitivity during pubertal maturation could be a potential mechanism for the perimenarchal abnormalities seen in hyperandrogenemic adolescents who appear to exhibit early manifestations of PCOS. The mechanisms underlying the reduced hypothalamic sensitivity, however, and remain unclear. The potential roles of hyperinsulinemia and hyperandrogenemia often present in women with PCOS, in modifying ovarian steroid regulation of the GnRH pulse generator have to be clarified, although an intrinsic abnormality could not also be excluded. Luteinizing Harmone. Classic studies in primates have demonstrated that pulsatile secretion of GnRH is an important prerequisite for normal pituitary function and that the regulation of gonadotrophin levels is controlled by ovarian steroid feedback on the anterior pituitary cells. Thus, low levels of estrogen inhibit LH and FSH at the pituitary level; FSH more than LH. High levels of estrogen exhibit positive stimulatory feedback with LH, inducing the LH surge at midcycle, whereas high steady levels of estrogen lead to sustained elevated LH secretion. In addition, low levels of progesterone acting at the level of the pituitary gland enhance the LH response to GnRH and are responsible for the FSH surge at midcycle. As a consequence, the question of whether the gonadotropin abnormalities seen in PCOS might be secondary to an estrogenic effect on the pituitary or even more to an effect of androgens, independent of their aromatization to estrogens, at the level of the hypothalamus and/or the pituitary has been considered. Although the data are inconsistent, they mainly suggest that if a primary abnormality of serum sex steroids concentrations has a stimulatory effect on LH secretion in PCOS, this effect must be minimal. In addition, raising serum androgen concentrations in normal women or women with the PCOS do not stimulate the secretion of luteinizing hormone. An additional consideration reported is that the pattern of gonadotrophin responses to GnRH agonist administration in PCOS women appears to be "masculinized." Recent data support the hypothesis that perinatal exposure of the neuroendocrine axis to excess levels of androgen may bring about such masculinization by programming the neuroendocrine system to secrete excessive LH at puberty, thus resulting in ovarian HA. This hypothesis has been further supported in primate studies, which show that prenatal exposure of female rhesus monkeys to testosterone propionate increases serum LH levels in adulthood.

Ovarian defect

A number of authors have proposed an alternative model of PCOS as a form of gonadotropin-dependent ovarian HA in which the central abnormality is an elevated intraovarian androgen concentration. They presented data suggesting that women with PCOS have increased the formation of 17α-hydroxyprogesterone and androstenedione in response to LH due to abnormal enzymatic regulation (dysregulation) of steroidogenesis. In a subsequent *in vitro* study using a primary monolayer culture system of human thecal cells, they demonstrated a significant increase in both basal- and LH-stimulated androstenedione production per cell in theca from polycystic ovaries compared to the response in normal ovaries, although the magnitude of response to LH was similar. Importantly, the addition of LH *in vitro* did not significantly alter the androstenedione/progesterone ratio, suggesting that these observations cannot be explained solely by the exposure of thecal cells to high concentrations of LH *in vivo*. More recent studies from the group of Strauss and MacAllister have also shown that increased androgen production is a stable steroidogenic phenotype of PCOS theca cells propagated in long-term culture, strongly supporting the hypothesis that the hyperandrogenemia associated with PCOS results from an intrinsic abnormality of ovarian theca cell steroid genesis.



Pathophysiology of polycystic ovary syndrome

SYMPTOMS

Symptoms of PCOS

Women with polycystic ovaries and no other features of PCOS are regarded as asymptomatic and do not report an increased time to conceive. However, they do demonstrate a predisposition toward the development of ovarian hyperstimulation syndrome (OHSS).

Menstrual disturbance

In the largest series of women with PCOS, it is reported that of the 1871 women with at least one symptom of PCOS (using the older diagnostic criteria), approximately 30% had a regular menstrual cycle, 50% had oligomenorrhoea, and 20% were amenorrhea. Consequently, the majority of women with PCOS have an abnormal menstrual cycle, and the most frequent pattern is infrequent menstruation associated with ovulation.

Goldzieher and Green suggested that approximately 85–90% of women with oligomenorrhea, and up to 30–40% of those with amenorrhea, will have PCOS. Obesity appears to augment anovulation in PCOS through increased peripheral estrogen production and increased pancreatic insulin production interfering with the hypothalamic–pituitary–ovarian (HPO) axis and resulting in elevated LH levels, which interfere with follicular maturation. Weight increase might induce oligo- or amenorrhea, and weight loss can restore ovulation and regular cycles.

Obesity

The reported prevalence of obesity in women with PCOS depends, to a large extent, on the type of clinic to which the patient presents and on the diagnostic criteria used. However, in most large studies, 35–50% of women with PCOS are overweight (BMI >25) or obese (BMI >27 kg/m^2). Abdominal adiposity is common, with an increased waist-hip ratio. Obesity increases the risk for type-2 diabetes, and up to 30% of obese PCOS women have IGT, and a further 7.5% will develop frank diabetes by their forties. Central obesity is thought to be a significant factor leading to the seven-fold increased risk of myocardial infarction in women with PCOS. However, the beneficial effects of weight loss are consistently shown, in improving menstrual cycle frequency, restoring ovulation, and normalizing biochemical indices, particularly IR. Due to the high prevalence of IGT and type-2 diabetes among obese women with PCOS, the consensus group advocates the screening of obese women (BMI >27 kg/m^2) with PCOS with an oral glucose tolerance test.

The association of obesity and PCOS is not completely understood, although it is known that in addition to raised serum insulin, LH and androgens, hypothalamic endorphins, and leptin are raised in anovulatory overweight women. However, on losing weight, the LH pulse frequency and amplitude and the leptin levels do not appear to alter before the resumption of menstruation.

Hirsutism

Hirsutism in women describes the growth of terminal hair in an adult male distribution. Common presentations are excess facial hair, hair on the chest between the breasts, and hair on the lower abdomen. Hirsutism is affected by familial and racial factors. They described a prevalence of "abnormal" Ferriman–Gallwey scores of at least 6, 8, and 10 in the unselected female population of 8.0, 2.8, and 1.6% in women and 7.1, 6.1, and 2.1% in women. In those with PCOS, the incidence was as high as 70%. The prevalence and extent of hirsutism are partially racially determined, and it is more common with darker skin and rare in Japanese women with PCOS. Hirsutism in PCOS reflects androgen excess, predominantly local dihydrotestosterone (DHT). The dermal papillae express androgen receptors that directly influence the size of the hair follicle and hence the hair produced. Weight loss has been shown to reduce hirsutism. Exogenous estrogens (such as the combined oral contraceptive [COCs] pill) will suppress ovarian androgen production and stimulate SHBG, hence reducing free circulating testosterone.

Androgenic alopecia

This describes the progressive pattern of loss of scalp terminal hair that is common with baldness in men and much less common in women, although probably underdiagnosed in those with PCOS. To present with alopecia requires a familial predisposition to baldness and an associated increase in circulating androgens, consequently not all women with an excess of circulating androgens will suffer from androgenic alopecia. A recent study of 89 women, of mixed ethnic origin, with androgenic alopecia, demonstrated a 67% incidence of polycystic ovaries. The control group of women had polycystic ovaries in 27% of cases, consistent with previous studies. Of women with androgenic alopecia, 21% were also hirsute, compared with 4% of the control group. Interestingly, the women with alopecia had higher testosterone, androstenedione, and free androgen index than controls, but few had frankly abnormal androgen levels.

Acne

Acne is an inflammatory disorder of the hair follicle and its associated sebaceous and apocrine gland. It is present in up to one-third of women with PCOS. Unlike androgenic alopecia and hirsutism, the principal problem for women with acne is an increased sebaceous secretion, and serum androgen levels are often not raised.

Acanthosis nigricans

Acanthosis nigricans is a mucocutaneous eruption that occurs most frequently in the axillae, skin flexures, and the nape of the neck. It is manifest by increased pigmentation and papillomatosis. It is a marker associated with IR and compensatory increased insulin secretion. It is thought to be present in women with PCOS in between 1 and 3% of cases 14, 44 and may present more commonly in adolescents with PCOS [21].

TREATMENT

Treatment options for targeting common symptoms

COCs having long been used as the first-line treatment in PCOS management, COCs offer not only menstrual regulation and endometrial protection but also a benefit against cutaneous stigmata of HA in women with PCOS. Mechanisms whereby COCs mediate improvements in PCOS-related symptoms include:

- A suppression of pituitary luteinizing hormone (LH), thereby reducing the stimulant effect of LH on androgen production by the ovarian theca cells;
- An increase in hepatic SHBG directly resulting from the estrogen component in the COC; the net effect is a decline in the free androgen levels and hence an improvement in the clinical features of HA (e.g. acne and hirsutism); and
- The antiproliferative effects of the progestin component of the COC formulation, which offers protection against proliferative endometrial pathologies that oligomenorrheic and insulin-resistant women are particularly at risk of.

In those with excess body mass, the use of progestins alone (when administered orally or through intramuscular, subcutaneous, or intrauterine delivery routes) can be efficacious in mitigating the risk of endometrial pathologies (such as endometrial hyperplasia and cancer) that are recognized in the setting of chronic anovulation and long-term exposure to unopposed estrogen (endogenous or exogenous). The successful use of intrauterine progesterone-releasing systems in cases of endometrial hyperplasia and early stages of endometrial cancer has also been described. Anovulatory and oligomenorrheic women who are deemed at a disproportionately higher risk of estrogen-related risks (such as thromboembolism) may thus benefit from a progestin-only approach, as a strategy for managing the commonly encountered dysfunctional uterine bleeding and as prophylaxis against the risk of endometrial cancer.

Treatment options for managing infertility impaired functioning of the HPO axis is well recognized to underlie the OD of PCOS [22].

Clomiphene-citrate (CC)

CC is conventionally considered as the first-line treatment for the management of the normogonadotropic anovulation seen in PCOS. A selective estrogen receptor modulators (SERM), CC binds to and acts as an estrogen antagonist at the hypothalamic-pituitary estrogen receptors, thus abrogating the estrogen-mediated suppression of pituitary gonadotropins; an increase in the endogenous release of FSH thus ensues and is responsible for initiating and maintaining ovarian follicle recruitment, growth, and subsequent ovulation. Per conventional protocols, CC is started at doses of 50–150 mg daily for 5 days (starting on days 3–7 or 5–9 of the cycle). Recent data suggest that an extended regimen (CC for 10 days) may be efficacious in some patients not responding to the traditional dosing regimen.

Tamoxifen

Tamoxifen, a sister SERM, may be an option in the subgroup of patients who fail to either ovulate or conceive with CC. Antiestrogenic effects of CC at the level of the endometrium and cervical mucus are suggested as mechanisms that may explain the relatively suboptimal pregnancy rates (30–40%) seen with CC, despite evidence of an ovulatory response in almost 80% of the treated population.

Aromatase inhibitors

The latest addition to the armamentarium of ovulation-inducing agents, aromatase inhibitors (AIs) is increasingly being incorporated into the clinical paradigm for managing ovulatory infertility. They act in a manner similar to, and yet are distinct from, SERMs. Inhibition of the enzyme aromatase results in profound reductions in serum and tissue estrogen levels, thus abrogating the estrogen-mediated negative feedback suppression at the hypothalamic-pituitary level; the net result is an increased release of pituitary FSH, which then induces follicular growth. Unlike CC, AIs do not have any adverse effects at the level of the endometrium. Letrozole and anastrozole are the two AIs that have demonstrated success with achieving ovulation induction in CC-resistant patients. Ovulatory response and pregnancy rates associated with AIs are comparable to those seen with CC, but comparative data are sparse. A head-to-head trial comparing the efficacy of CC and AIs in treating ovulatory infertility in women with PCOS is ongoing.

Gonadotropins

In patients who are resistant to, or fail to achieve success with, first- and second-line strategies such as SERMs and AIs, ovarian stimulation through exogenous gonadotropins is of proven efficacy in achieving ovulation and reproductive success, although at the risk of OHSS and multiple pregnancies. Individualized modifications of treatment protocols – including lower dose step-up, low dose step-down, and minimal stimulation combining CC and low-dose gonadotropin – have demonstrated success in mitigating these treatment-related risks in women with PCOS undergoing infertility treatment with gonadotropins.

Assisted reproductive technologies

Recent years have witnessed an expansion in the repertoire of strategies aimed at reducing the risk of OHSS in women undergoing IVF; these include preferential use of GnRH antagonist for ovulation suppression and the use of GnRH agonist instead of human chorionic gonadotropin to achieve ovulation triggering. *In vitro* maturation, while still regarded an experimental approach, offers a cost-effective strategy with minimal risk of OHSS wherein immature oocytes are recovered and allowed to attain maturity *in vitro* followed by insemination and subsequent embryo transfer.

Laparoscopic electrocautery of the ovaries (LEO) and/or laparoscopic ovarian drilling (LOD) for patients with PCOS who have failed to respond to attempts at ovulation induction with first- and second-line strategies such as SERMs and AIs, bilateral electrocautery of the ovarian surface offers a high likelihood of restoring ovulation. Although the underlying mechanisms are yet to be elucidated, reduction in the hyperandrogenic milieu follows LEO and/or LOD and are proposed to underlie the resumption of ovarian follicular growth. Spontaneous pregnancy rates within the year following LEO/LOD are comparable to those achieved with gonadotropin use but without the risk of multiple pregnancies. However, the need for surgery, with its concomitant risks, transient therapeutic efficacy, and the risk of inducing pelvic adhesions, limits the wider use of LEO/LOD in the management of ovulatory infertility in women with PCOS.

Antiandrogens

Given the risk of malformations, such as the feminization of a male fetus, linked with antiandrogens, there has to be an imperative need for reliable contraception if these agents are to be prescribed to women of reproductive age who may be at risk of an unplanned pregnancy. Antiandrogen therapy must be discontinued at least 3 months in advance of attempting conception.

Spironolactone

An aldosterone antagonist recognized for its antihypertensive and potassium-sparing diuretic effects, spironolactone is of proven efficacy against acne, and to a lesser extent against hirsutism related to PCOS. Its mechanisms of action include a reduction of adrenal gland testosterone production through depletion of microsomal cytochrome p-450, the competitive inhibition of the androgen receptors in the target tissue, and the inhibition of 5-alpha-reductase (the enzyme responsible for the conversion of testosterone into the more potent DHT).

Flutamide

A nonsteroidal competitive antagonist of androgen binding to the androgen receptor, flutamide has been studied in the PCOS population and has demonstrated efficacy against acne and hirsutism. A risk of serious hepatotoxicity, however, limits its use in the clinical management of PCOS.

Finasteride

A 5-alpha-reductase II inhibitor that blocks the conversion of testosterone to its more potent form DHT, finasteride has shown promise in the management of PCOS-related hirsutism. At doses of 1–5 mg/day, the drug is well tolerated and relatively safe when used to manage symptoms of HA. However, this agent is not currently approved for use in women. A study that sought to compare objectively spironolactone (100 mg/day), flutamide (250 mg/day), and finasteride (5 mg/day) in the treatment of hirsutism in 40 women found equal clinical efficacy for the three drugs others, however, demonstrated spironolactone to be superior to metformin and finasteride in the treatment of hirsutism in women with PCOS. Others again have shown that the combination of spironolactone and COCs offers synergistic efficacy against hirsutism.

Eflornithine hydrochloride

Eflornithine hydrochloride is an inhibitor of the enzyme ornithine decarboxylase in human skin. Its topical application has been shown to slow down the growth of hair in treated areas. Adverse events are limited to the application area and include sensations of burning, stinging, and tingling.

Glucocorticoids

Glucocorticoids in low doses may offer cutaneous benefit for those with hyperandrogenemia not responsive to the more commonly used strategies.

Cyproterone acetate (CA)

CA is a synthetic steroid that binds to the steroid receptors, exerting progestogenic, antiandrogenic, and weak glucocorticoid-like activity. In combination with ethinylestradiol in AaCOC formulations (not available in the US), this agent has demonstrated efficacy in treating hirsutism in women with PCOS. In COC formulations, CA is used at a 2 mg dose.

Although generally well tolerated, it has side effects including weight gain, edema, decreased libido, and headaches.

Treatment options for managing metabolic abnormalities

Insulin-sensitizing drugs

Hyperinsulinemia and IR are recognized as being of pathophysiological relevance for the endocrine and metabolic milieu of PCOS. They are further recognized to contribute to the HA of PCOS. In turn, the local androgen excess within the ovaries contributes to the ovarian follicular arrest that underlies the polycystic appearance of ovaries, a hallmark of the syndrome. Beyond its causative role in PCOS symptomatology, IR is central to the processes that underlie the predisposition of women affected by PCOS to long-term comorbidities including type-2 diabetes, CVD, and endometrial pathologies. Given this last fact, insulin-sensitizing strategies (including both pharmacotherapy and lifestyle modifications) are commonly used in the management of PCOS.

Metformin

A safe and well-tolerated drug that is of proven efficacy in the management and prevention of type-2 diabetes, metformin is one of the insulin-sensitizing drugs most commonly used in the management of PCOS. Its mechanism of action centralizes around a metabolic pathway through a decrease in hepatic gluconeogenesis through activation of the AMP-kinase pathway. Improved ovulation rates are observed in a variable proportion of women with PCOS treated with metformin. An early meta-analysis that included randomized controlled trials (RCTs) investigating the effect of metformin compared with either placebo or no treatment, or with an ovulation-inducing agent in women with PCOS, demonstrated that metformin alone was effective in achieving ovulation in 46% of recipients compared with 24% in the placebo arm. In addition, when metformin was added to CC, 76% of the recipients in the combination arm achieved ovulation compared with 42% receiving CC alone (number needed to treat = 3.0). Metformin's efficacy as an ovulation-inducing agent was, however, subsequently refuted in a large RCT that compared the efficacy of metformin or CC alone versus a combination of the two in achieving ovulation, pregnancy, and live birth. Metformin alone emerged as a poor strategy for managing ovulatory infertility compared with CC; however, improved ovulatory and live birth rates were observed in the combination group, suggesting a role for metformin as an adjunct to CC in managing ovulatory disorders of PCOS.

Thiazolidinediones (TZDs)

TZDs belong to a family of peroxisome proliferator-activated receptor gamma (PPAR-g) agonists and act primarily by increasing peripheral glucose uptake. The PPAR-g is identified as a transcription factor that regulates adipogenesis as well as being involved in systemic insulin action. The efficacy of TZDs in ameliorating IR and hyperinsulinemia and in improving ovarian HA has been observed in women with PCOS. Similar to metformin, the effects of TZDs on ovarian function and ovarian follicular development in PCOS have been studied, but with results that are less promising than those obtained with metformin alone.

Incretins

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are recently recognized regulators of insulin response and insulin signaling, particularly following meal ingestion. The impaired incretin effect is appreciated in states of IR including type-2 diabetes; conversely, oral dipeptidyl peptidase-4 (DPP-4) inhibitors and the parenterally administered GLP-1 agonists have demonstrated therapeutic efficacy in improving glycemic control in type-2 diabetics. Recent studies have demonstrated lower GIP levels in obese women with PCOS. Given that IR is of pathophysiological relevance to the endocrine and metabolic dysfunction of PCOS, the therapeutic benefit of incretin therapy in this population is plausible.

DPP-4 inhibitors

DPP-4 inhibitors (sitagliptin, linagliptin, vildagliptin, and saxagliptin) act by inhibiting the activity of DPP-4, the enzyme that rapidly converts GLP-1 to its inactive state. Studies of sitagliptin therapy in type-2 diabetes have demonstrated efficacious glycemic control when added to either metformin or a TZD – the former having the advantage over TZDs of not causing weight gain. Sitagliptin is currently approved as an adjunct to diet and exercise, either as monotherapy or in combination when the initial agent, such as metformin or pioglitazone, does not provide adequate glycemic control.

GLP-1 agonists

GLP-1 agonists differ from the oral DPP-4 inhibitors in that they need to be injected. Commercially available GLP-1 agonists are exenatide and liraglutide, but many additional ones are under development. Exenatide improves glycemic control while reducing body weight and maintaining low rates of hypoglycemia. Liraglutide injected once daily has been shown to improve glycemic control in individuals with type-2 diabetes (up to a 1.5% decrease in glycated hemoglobin) when used as monotherapy or in combination, while simultaneously decreasing weight. A single study has explored the therapeutic efficacy of exenatide in the PCOS population, with encouraging results. In this 24-week trial undertaken in 60 overweight oligo-ovulatory women with PCOS aged 18–40 years, participants were randomized to one of three treatment groups for 24 weeks: Metformin alone at 1000 mg twice daily, exenatide alone at 10 μg twice daily, or a combination of the two drugs.

Acarbose

The therapeutic efficacy of acarbose is attributable to its action on reducing glucose absorption in the gut and thus decreasing post-prandial insulin levels. The potential role of acarbose in PCOS has been studied, but its effects on insulin sensitivity parameters, body mass, and vascular function were inconsistent, and there was no significant improvement of PCOS-related dyslipidemia. Adverse effects, predominantly gastrointestinal, are common, and potentially fatal hepatotoxicity has been reported. Inconsistent efficacy, bothersome side effects, and the risk of liver damage limit the role of this agent in clinical practice.

Inositol stereoisomers

Inositol is a member of the Vitamin B complex family; two of its stereoisomers, D-chiro-inositol (DCI), and myo-inositol (MYO) have been studied to determine whether they can improve insulin sensitivity and hence whether they are relevant in PCOS management. Although earlier data had identified DCI as potentially efficacious, subsequent data failed to confirm its efficacy in PCOS. MYO, however, has shown consistent promise.

Lipid-lowering agents (statins)

Elevated serum LDL and triglycerides and suppressed high-density lipoprotein levels are commonly encountered in women with PCOS. 1–3, Statins inhibit cholesterol biosynthesis, decreasing circulating LDL cholesterol, and offer logical therapeutic benefit for the dyslipidemic women who are deemed at an enhanced risk of CVD. The use of statins is associated with a 20% decrease in cardiovascular mortality per mmol/l of LDL cholesterol reduction achieved.

Miscellaneous

Opioid receptor antagonist

The rationale behind the use of opioid receptor antagonists in PCOS is based on the existing evidence of sympathetic overactivity and elevated β-endorphin release, phenomena that directly influence the release and action of insulin. Naltrexone is an orally administered competitive non-selective opioid receptor antagonist and has been studied in the PCOS population with encouraging, although inconsistent results. A significant improvement in insulin sensitivity indices has been

described with the use of oral naltrexone in hyperinsulinemic women by some, but not all. Gastrointestinal side effects are common and there is a risk of drug interaction with common medications, which limits the use of opioid receptor antagonists in clinical practice.

Orlistat

A gastric and pancreatic lipase inhibitor, orlistat reduces the absorption of dietary fats by inhibiting the hydrolysis of triglycerides. Its efficacy in obesity is well established; its use in PCOS has been explored, with evidence of metabolic benefit. Improved parameters of insulin sensitivity and decrease in body mass were evident in PCOS patients following treatment with orlistat combined with dietary modification. At the commonly employed dosing regimen of 120 mg 3 times a day by mouth during or within an hour of consuming a fat-containing meal, side effects are commonly encountered and include fecal urgency and incontinence, fatty stools or discharge, diarrhea, abdominal discomfort, and flatulence. Possible drug interactions must be considered, and ensuing malabsorption may impair the absorption of orally administered medications and fat-soluble vitamins. While orlistat may have a role in the management of PCOS-related obesity, its relevance for managing the endocrinopathy of PCOS is questionable.

Vitamin D

Vitamin D insufficiency has been related to obesity, dyslipidemia, MetS, hypertension, and diabetes, and accruing data suggest that Vitamin D deficiency may be of relevance to the endocrinological and metabolic milieu of PCOS. An inverse relationship between circulating levels of 25OHD (a metabolite of Vitamin D that reflects an individual's Vitamin D status), androgens, and insulin sensitivity is described. Limited data suggest an improvement in insulin sensitivity parameters and menstrual cyclicity following Vitamin D supplementation. These findings merit substantiation inappropriately designed RCTs before Vitamin D can be added to the list of agents with proven efficacy for the management of PCOS.

LITERATURE REVIEWS

The fundamental defect of PCOS remains unknown and an area of ongoing study. There is a growing consensus that the key features include IR, androgen excess, and abnormal gonadotrophin dynamics. A familial pattern in some cases suggests a genetic component, but the candidate genes are yet to be identified. There are links between PCOS and endometrial cancer, obesity, CVD, and DM with both short- and long-term consequences. Although the adverse health consequences associated with PCOS are substantial, unfortunately, most women are not aware of these risks. Early recognition and treatment of the metabolic sequelae of PCOS should be the focus of the clinician. Lifestyle modifications, mainly a balanced diet, and regular exercise, are of utmost importance. Metformin has been increasingly used as an effective pharmaceutical treatment of PCOS and soon will take place in the routine management of both short- and long-term consequences of this disorder [22].

PCOS is the most common endocrine disorder of women in their reproductive years. It also has a huge implication for society as a whole, as these women are at an increased risk of obesity, have a markedly increased risk of diabetes and death after a myocardial event and might also be at long-term risk for other CVD. A recent consensus meeting has led to the formulation of unifying diagnostic criteria for the definition of PCOS to enable an internationally agreed terminology to be used. These criteria rely on the presence of two of the following:

I. Oligo-/anovulation;
II. Clinical or biochemical evidence of HA; and
III. The presence of polycystic ovaries.

It is found that AMH levels were significantly higher in PCOS patients with HA than without HA; indicating that HA is associated with an extra increase in AMH. This may reflect the severity of the disruption of folliculogenesis in patients with HA. Serum AMH levels may be related to the severity of the syndrome because they have been observed to be higher in women with insulin-resistant PCOS that inpatients with normal insulin sensitivity.

It is now undeniable that serum AMH is a valuable tool for the diagnosis of PCOS. However, it must be noticed that the thresholds for high serum AMH level have to be reviewed and validated worldwide. There is a lack of well-defined population and some other matters such as stability and heterogeneity of circulating AMH, wide range of values, inter-laboratory variability, and different immunoassay used worldwide, but AMH can be introduced as criteria for PCOS diagnosis.

The study was conducted on 150B.Sc. nursing students to assess the knowledge regarding PCOS. Students above 18 years of age were included in this study. Most of the students were in the age group of 21–25 years (85%). The analysis was done by frequency percentage. The level of knowledge was categorized into poor (13.3%), average (76.0%), and good (10.7%). The finding of the study shows that the majority (114) of students had average knowledge.

Due to the varied nature of PCOS and the large range of possible signs and symptoms, health personnel need a thorough knowledge of the disorder and its management. Nurses should be aware of the various organizations which render support. Counseling for adolescents should be included in the curriculum which will provide awareness of the disorder and lifestyle modification. In this study, the 2–3 years BSc. (N) students had average knowledge on PCOS [23].

PCOS among adolescents is an emerging problem that needs careful assessment, timely intervention, and appropriate treatment. To the best of our knowledge, this is the first urban community-based study in India, estimating the prevalence of PCOS among the relatively younger population with a much lower mean age unlike reported earlier. As Rotterdam criteria are much more broad-based and do not necessarily require evidence of HA, the prevalence by Rotterdam criteria (22.5%) was almost double compared to that using AES criteria (10.7%). If all the enrolled girls would have participated in the study, the prevalence could further reduce as most girls who did not come for further investigations were symptom-free. The prevalence figures among the older age groups are slightly high especially considering the AES criteria, probably indicating an increase in HA with age and hence diagnosis and timely intervention could possibly reduce the morbidities in older age groups. This prevalence is relatively higher than that reported by most studies, mainly due to the use of different diagnostic criteria, study settings, age groups of the sample studied and hence cannot be compared.

Puberty is a period when there are physiological HA and hyperinsulinemia which mimics some features of PCOS from Tanner Stages I–III with return to the prepubertal stage by Tanner Stage V. Hence, we enrolled girls 2 years post-menarche when H-P-O axis settles down to normal. Due to this transitory appearance of symptoms and signs of PCOS during adolescence, care must be taken to avoid premature labeling of a case as PCOS to avoid overtreatment and psychological stress. Presence of oligomenorrhea among adolescent girls, 2 years post-menarche, can be a good screening indicator to diagnose a probable case of PCOS as reported earlier. A diagnosis is confirmed if all three signs/symptoms of PCOS are present which was observed in 27.4% of PCOS cases in the study. The diagnosis may be considered but not confirmed among those who have two signs/symptoms and this phenotype in our study was 63% which is being followed-up for the emergence of confirmed PCOS or settling down to normal HPO axis. Free testosterone assays are not reliable, and the accurate ones are complicated, expensive, and labor intensive. Hence, FAI is a better marker of free testosterone, but as observed in our study it is more correlated with the degree of obesity. Adolescent obesity and PCOS individually and together have emerged as important public health issues in India.

The feasibility of conducting such community-based study justifies the need to upscale this effort to get an overall estimate of the disorder

in a diverse sociocultural and economic background, providing an opportunity for early detection and prevention of morbidities among adolescents and young women in India [24].

There is limited evidence directly related to multidisciplinary PCOS clinics and the efficacy of their treatment. It is well accepted that PCOS is multifaceted and has a high degree of heterogeneity among individuals with the syndrome. When treating a patient with PCOS, it is important to focus on treating the patient's initial needs while decreasing the risk of long-term risk factors. Symptoms will be better treated if the patient is treated by a variety of specialists all working together. When individuals are exposed to multiple providers, it is less likely that a PCOS diagnosis will go unseen. The sooner PCOS is identified and treatment is initiated the quality of life and prognosis of the syndrome will improve. The perceived benefits of multidisciplinary clinics globally include improved patient satisfaction, greater weight loss, improved body image, and better management of PCOS from a holistic standpoint. Further research is needed to assess additional existing multidisciplinary clinics to determine patient satisfaction and treatment prognosis compared to those seeking treatment from only one provider. More research is also warranted to gain a better understanding of evidence-based guidelines for the treatment of PCOS, especially when considering dietary recommendations [25].

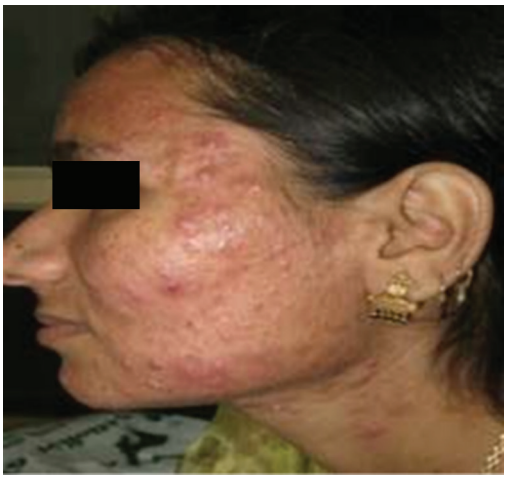
As is evident from the summarized literature, a vast array of pharmacotherapies with varying potential benefits is available for the management of PCOS. It is imperative to appreciate that no single agent may address the entire spectrum of concerns (endocrine, metabolic, and clinical) that may present in a woman diagnosed with PCOS given the heterogeneous nature of the syndrome. Hormonal strategies such as COCs can efficaciously address menstrual irregularities, offer cutaneous benefits against hyperandrogenic symptoms, and offer endometrial protection against the development of proliferative pathologies, yet it will not mitigate the metabolic abnormalities of PCOS. Similarly, antiandrogen therapy primarily targets cutaneous stigmata of HA and may improve menstrual cyclicity as a secondary outcome; given a possible improvement of ovulatory response with antiandrogen therapy as well as a recognized teratogenic potential, adherence to a reliable contraceptive option is to be stressed when offering antiandrogen therapy to women with PCOS. The safety and efficacy of metformin in offering metabolic benefit in PCOS are well established. Although far less effective than CC as an ovulation-inducing agent, metformin used as an adjunct to ovulation-inducing strategies may improve reproductive outcomes, particularly in obese women with PCOS, and enhance response to treatment in those deemed resistant to CC. TZDs offer little benefit over metformin in the treatment of PCOS-related IR and are to be avoided in women seeking pregnancy. While metabolic benefits and improvement in PCOS-related hyperandrogenemia are superior with statins than with metformin alone, statins, similarly to TZDs, are to be avoided in women seeking pregnancy. Incretins are a promising class of metabolic modulators and merit further investigation in the PCOS population. The use of MYO is a safe and simple strategy that has shown efficacy against biochemical and clinical endpoints in PCOS management and merits further consideration [26].

In conclusion, PCOS is becoming a more prevalent disorder among women of reproductive age with lifelong complications. One of the most challenging aspects of this syndrome is its ambiguous diagnostic criteria and the vast complexity of characteristics. In the future, more research in the genetics and pathophysiology of PCOS is needed to determine preventative risk factors as well as successful treatment modalities for this syndrome [27].

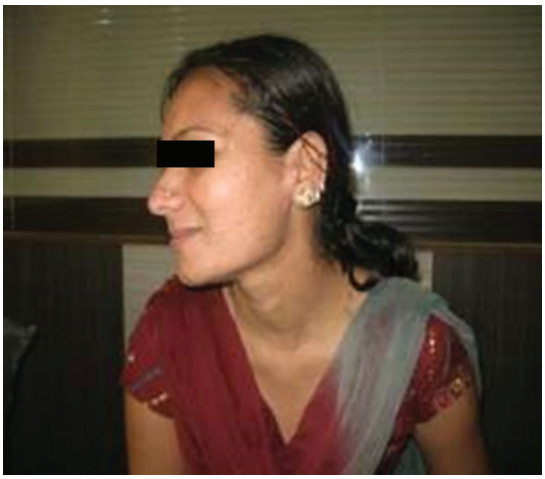
Women with PCOS have several risk factors for developing type-2 diabetes, including central obesity, abnormalities in insulin action and secretion, family history of type-2 diabetes. They also have increased levels of cardiovascular risk factors: IR, obesity, dyslipidemia, and hypertension. Menstrual irregularity may be an additional risk factor [28].

According to Ayurved, PCOS is equated to Artavakshaya. It is a disorder involving Piita, Kapha Dosha, Meda, Rasa dhatu, and artava upadhatu. Therefore, in this disease, the involvement of Dosha, Dhatu, and Mala is seen. The main vitiation of Vata is done and Yogabasti regulates Vata Dosha and regulates H-P-O axies.

Before treatment



After treatment



It can be concluded that all female patients of acne should be screened for PCOS by history and examination if necessary. Ayurvedic therapy can have successful treatment of the acne with PCOS. Remarkable decrease in acne with normal menstrual cycle proves success [29].

Potential areas of further research activity include the analysis of predisposing conditions that increase the risk of PCOS, particularly genetic background and environmental factors, such as endocrine disruptors and diet. In addition, defining alterations of steroidogenesis in PCOS need to be re-examined to quantify ovarian, adrenal and extraglandular contribution, as well as a change in the blood androgen reference values due to the expanding use of mass spectrometry. Clearly identifying premenarchal and post-menopausal phenotypes of androgen excess and PCOS would significantly enhance our epidemiologic studies of natural history and intervention studies. Intraovarian regulation of follicle development and mechanisms of follicle arrest and the impact of metabolic abnormalities on these processes, as well as molecular mechanisms by which insulin excess regulates androgen secretion and metabolism and disrupts follicle development are other potential issues for investigation. Current information would suggest androgens alone may be necessary but not sufficient to cause follicular arrest, and it is likely that other inhibitors and nonsteroidal directed pathways are implicated in follicular arrest. Future studies should not only utilize

both existing cell culture and animal models discussed above but also utilize ovarian follicles grown and matured in 3-D matrices or created out of stem cells.

The concept that androgen excess may be responsible for the development of IR also needs to be re-examined, since studies performed in the last decade in experimental animals have supported the hypothesis that early exposure to modest androgen excess may favor the development of IR and enlarged visceral adiposity, although available data in humans are still sparse and controversial and preliminary prospective data in humans seem to not support this hypothesis. There have been a number of recent well-designed adequately powered trials examining infertility treatment in women with PCOS. While this is a positive development, it is only a start. PCOS status is expected to lead to many long-term consequences in women, specifically the development of type-2 diabetes, CVDs, and hormone-dependent cancers. Identifying susceptible individuals would help to individualize therapeutic and, possibly, preventive strategies [30].

NEWER ADVANCEMENT

Current research and future perspective

During the past 5 years, there have been over 3172 articles published related to PCOS, with an increasing number of articles published each year. Of these articles, the topics of IR and metabolic abnormalities associated with PCOS were the most researched.

Diagnosis

As described in section 4.1, there are several challenges in confirming the diagnosis of PCOS in women who present its characteristics symptoms. Although HA testing is the most promising diagnostic criteria, as it is seen in 60% of women with PCOS, its methods of assessment could result in diagnostic inconsistency. The dilemma with the presence of hirsutism is that it is difficult to create a distinct profile of characteristics associated with PCOS. Clinically, HA is most often diagnosed through the presence of hirsutism. Other indicators such as acne and alopecia are occasionally taken into account. However, the biggest drawback of using hirsutism as a primary indicator of PCOS is its subjective assessment. It has been shown that women of different ethnicities display varying degrees of hirsutism, and symptoms are especially rare in Asian women and not well understood in adolescent patients. The second test to diagnose HA is to measure circulating androgen levels.

RESULTS

Our study demonstrated that PCOS cases were on the higher scale of the normal range for biochemical parameters, especially obese PCOS had higher mean values compared with their lean counterparts suggesting pertinent danger to jump off the thin line and turn into MetS with increasing age as is already known. Hence, in overweight/obese cases, lifestyle and dietary changes along with exercises for weight management must be recommended, coupled with medical management to treat clinical symptoms and hyperinsulinemia.

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