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Review Article

A Misnomer, Polycystic Ovarian Syndrome, In Adult and Perimenopausal Women *De Novo* or Continuation from Adolescence!

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Abstract

Introduction: There is scarce information about polycystic ovarian syndrome (PCOS) in adult, perimenopausal women. Symptoms are deceptive because of physiological changes at this age and due to multiorgan and multi system involvement. Overproduction of ovarian androgen, and Luteinizing hormone, are common. Clinical picture includes Menstrual irregularities, Sleep apnea, Obesity, Male pattern balding, Acanthosis negricans, Insulin resistance, Hyperinsulinemia. Polycystic ovaries may or may not be there. As age advances there is risk of hypertension, cardiovascular disease, diabetes mellitus, and endometrial carcinoma too.

Objective: Information about PCOS in adult, perimenopausal women.

Methodology: With available search engines studies, reviews were looked into. Opinions too were searched and self experiences added.

Results and Conclusion: It is being believed that PCOS of adolescence might persist or PCOS might occur de novo in perimenopausal women though some believe that it disappears around menopause. However, it is more difficult to diagnose, because at this age menstrual abnormalities and obesity are common. Etiology, pathology, genetic to insulin lipid metabolism are not very well known. Anti-Mullerian hormone might be responsible for some abnormalities. Fasting glucose insulin ratio and free testosterone are popular diagnostics, prevention has some limitations. Not much is known about efficacy of oral contraceptive pills in perimenopausal women though they are commonly used in adolescents and young women. Insulin-sensitizing agents can ameliorate IR, endocrinal, metabolic abnormalities. Metformin does lead to weight loss but dose not increase insulin secretion or hypoglycaemia. Attempts need to be made for prevention of obesity, diabetes. cardiovascular, disease, endometrial cancer. Long-term follow-up is essential.

Keywords: *Polycystic Ovarian Syndrome; Adult, Premenopausal Women; Challenges*

Introduction

Polycystic Ovarian Syndrome (PCOS) of young women might linger in adult and perimenopausal women. However, it might occur *de novo* beyond young age, though it is believed by some that PCOS disappears around menopause. Such women are believed to be at risk of other serious disorders beyond reproductive dysfunction, depending upon their organ/system most affected. Hirsutism, hair loss,

weight gain, diabetes, hypertension, and endometrial cancer are common. Further it is being opined that PCOS is not just a gynaecological disorder but endocrine-metabolic disorder that has several consequences to woman's health. This enigmatic entity seems to affect one in ten women [1]. Studies revealed that the impairment of insulin sensitivity, impaired glucose metabolism, enhanced ovarian androgen secretion, and chronic inflammation observed in perimenopausal women with PCOS persist after menopause, with higher risk of Type 2 Diabetes Mellitus (T2DM). Metabolic syndrome (MBS) and Cardiovascular disease (CVD) [2].

Objective of the Study

To understand about challenges in diagnosis and management of PCOS in adult and perimenopausal women.

Results

Challenges in defining

As there are differences in criteria used for diagnosis of PCOS, standardization is difficult and so to define also. Women with (1) hyperandrogenism and/or hyperandrogenaemia, (2) oligo-ovulation/anovulation (3) exclusion of disorders known to cause similar symptoms and signs, continue to be diagnosed as PCOS. However, some experts suggested that two of the three features: (1) oligo-or anovulation (2) clinical and/or biochemical signs of hyperandrogenism and (3), polycystic ovaries (PCO), excluding other disorders which could cause these problems are sufficient [3-5]. This has expanded the NIH definition of1990. There are two phenotypes (1) ovulatory women with PCO and hyperandrogenism (2) oligo-anovulatory women with PCO, without hyperandrogenism (2) oligo-anovulatory women with PCO, without hyperandrogenism. Probably the second type is more frequent in later age [2-4]. Some women have PCO but no PCOS and others have PCOS but no PCO. So research continues.

Challenges in knowing incidence

There are reports which say PCOS can affect 2 to 8% of population [3,4]. Azziz., *et al*. [5] studied 400 unselected consecutive women of 18 - 45 yrs of age and reported prevalence of 6.6%. Ealier Miller [6] reported the rates of PCOS in mothers and sisters of patients of PCOS as 24% and 32%, respectively. However, there are scarce reports of PCOS in adult and perimenopausal women.

Dilemma in understanding etiopathology

The etiopathology of PCOS in adult and perimenopausal women is more difficult to understand. An autosomal dominant transmission likely. The heterogenicity of clinical and biochemical features can be explained by the interaction of a small number of key genes with environmental, and nutritional factors [7]. Though the genetic analysis of several candidate genes and gene regions-CYP11A yielded only modest results the recent information also suggested that PCOS might be a genetic disorder [8]. One study revealed that in women with oligomenorrhoea, hirsutism or hyperandrogenemia, family history of diabetes mellitus was present in 70%, hirsutism or menstrual disorders in 36 to 46% [9]. It might be because of hypersensitivity of the intra-ovarian-insulin-androgen signaling pathway in families. Dokras., *et al*. [10] reported that women with PCOS were likely to have a 11-fold increase in Metabolic Syndrome (MBS) compared with age-matched controls. So, it is believed that the condition runs in families. Sisters of those with the disorder are twice likely to have PCOS. Also, it may be combination of genetic and environmental factors which favor IR compensatory hyperinsulinemia, augmenting ovarian androgen synthesis. Insulin also triggers hyperandrogenemia by directly activating mitogenic pathways in ovarian cells and increasing transcription of steroidogenic acute regulatory protein (StAR) and several key steroidogenic enzymes. Increased androgens production from ovaries might in turn worsen IR, which leads to vicious cycle of IR hyperinsulinemia - hyperandrogenemia. Hyperinsulinemia frequency stimulates lipid storage with altered lipoproteins, cholesterol, hyperlipidaemia and obesity. Years back Frank [11] reported that the IR involved in pathogenesis of PCOS, marked in obese women, suggested a synergistic effect. However, IR is not just in obese women,

lean women can also have IR. Kidson [12] reported that IR was not due to hyperandrogenism, because androgen blockade reduced IR only by 10 - 15%. Amelioration of hyperinsulinemia is believed to result in a dramatic decline in circulating androgen. Many women with PCOS exhibited IR, but not all. Also, Conn [13] opined that insulin may not play a major role in the pathology of PCOS and hyperinsulinemia was probably an effect rather than causative agent in obese women. There seems to be link between elevated serum leptin and insulin to obesity in PCOS, contributing to the complexities of PCOS in obese women. Puurunen., *et al.* [14] have reported that premenopausal women with PCOS exhibited higher insulin levels as well as increased insulin response to glucose tolerance. They had increased HOMA-IR values, compared with controls. Furthermore, the whole- body insulin sensitivity index (ISI), described by Matsuda and DeFronzo [15] was decreased in perimenopausal PCOS. These findings were consistence with previous studies revealing that altered glucose metabolism was present in premenopausal women with PCOS. Shaw., *et al*. [16] found that women with self-reported irregular menstruation and biochemical evidence of hyperandrogenism had more IR and had more often T2DM compared with controls.

Puurunen., *et al*. [17] reported that impaired glucose metabolism, enhanced androgen secretion from ovary and chronic inflammation was observed in premenopausal women with which PCOS persisted after menopause also. The mechanism by which obesity caused IR was unclear. However, a post receptor defective insulin receptor signaling has been suggested. Legro., *et al*. [18] reported that hyperinsulinaemia increased ovarian androgen production by stimulating ovarian cytochrome P450c 17a, either directly or via LH. Insulin may potentiate the action of adrenocorticotropic hormone (ACTH) on adrenal steroidogenesis and contribute to hyperandrogenism through its inhibitory effect on hepatic SHBG production, increased the bioavailability of androgens, with increase in bound or unbound testosterone. Puurunen., *et al.* [17] reported decreased ovarian capacity to secrete 17-OHP, significantly enhanced in women with PCOS after menopause. This supported the results of a previous study [19] which revealed that perimenopausal women with PCOS exhibited increased adrenal androgen secretion compared with controls. The results of another study suggested that high serum testosterone was associated with an increased risk of CVD, but whether or not testosterone played a role as a marker or mediator in the process, was not obvious [20]. Azziz., *et al*. [21] and Goodarzi [22] have also suggested that women with POCS exhibited the overproduction of ovarian androgens, increased pituitary LH secretion, incomplete maturation of ovarian follicles, IR. and hyperinsulinemia. Leptin, an appetite-suppressing hormone was responsible for a partially overlapping message to the neurons, that critically controlled energy balance and therefore played a significant role in the regulation of body fat mass. Some researchers have reported that leptin levels were higher in women with PCOS [22], others reported levels similar to women with weight-matched controls [23]. Caro [24] and Fedoresak [25] also reported that the mean value of leptin was not different in women with PCOS compared to normal women, independent of obesity. However leptin deficiency and PCOS appear to have many similarities between their clinical, metabolic and biochemical features and more research was needed. Spritzer [26] reported that insulin and leptin levels correlated well, suggesting that insulin resistance and leptin deficiency could co-occur. Chronic inflammation, reflected by elevated levels of inflammatory markers, has been shown to be present, adding to the risk of CVD [27]. As such during menopausal transition, androgen levels remain stable or even rise and estrogen decreases dramatically. E1-Gharib [28] reported that Leptin contributes by creating chronic systemic inflammatory state which seems to be a feature of PCOS also. Ultimately, both IR and chronic inflammation have linkage to metabolic disturbances in PCOS, predisposing to T2 DM and CVD. Women with PCOS become more androgenic and so several features such as IR. chronic inflammation, abdominal adiposity, and dyslipidemia tend to worsen. So additive effects are possible. There is evidence that women with PCOS are at many times higher risk of developing T2 DM and CVD, dyslipidaemia and vascular dysfunction. However Wild., *et al.* [29] reported no direct evidence of increased incidence of CVD in middle aged women with PCOS, although the risk of stroke was slightly increased. In a recent study, adrenal androgen secretion was found to remain pronounced up to menopause indicating that exposure to hyperandrogenism persisted for a long time in these women [30].

Results of treatment with Metformin in obese and lean women with PCOS suggested that the reduction in ovarian and adrenal cytochrome p45017a- enzyme activity may be responsible for the amelioration of hyperandrogenemia in these women. Moreover, androgen seems to diminish highly oxidative and insulin-sensitive Type I Muscles fibres (TIMF) and increase glycolytic and less insulin-sensitive Type II Muscle fibres (TIIMF), further favoring the development of IR. Recent studies have suggested that Anti-Mullerian Hormone (AMH)

might in part be responsible for increased follicles-in the ovary. In women with PCOS, AMH may be negatively regulating the advancement of follies maturation. Women with PCOS have three fold higher circulating AMH levels compared to normal, reflected by increased growing pre-antral and small antral follicles, responsible for PCOS.

Diagnostic challenges

In addition to menstrual dysfunction, hyperandrogenism and a host of clinical, pathological and biochemical abnormalities coexist with PCOS. However related disorders need to be excluded for diagnosis. Because of hyperandrogenism and IR, the obesity in PCOS has been reported to be android (central) type with a waist-hip ratio of > 0.8 [31]. Taylor [3] reported obesity in 35 to 50%women with PCOS. Others reported features of male- pattern balding, acanthosis negricans, (darkened, thickened skin around the neck, armpits, or breasts), sleep apnea, hypertension. DM, endometrial cancer and CVD [32]. Balen., *et al*. [32] reported Hirsutism in 70%, but Taylor [3] reported less often frequency and gradual onset. Conway and colleagues [33] found Alopecia in 8% and Hirsutism of various degrees in 61% cases with PCOS identified at sonography. Taponen., *et al.* [34] reported PCOS in 37.3% of women who reported symptoms of oligomenorrhoea and hirsutism compared to 18.2% amongst controls. Overall, 12 to 22% of obese women described regular menstrual cycles, compared to 28 to 32% of normal weight women with PCOS. Acne has been reported in 25 to 35% patients. Hyperinsulinemia has been reported to be common pathogenetic factor for PCOS and MBS both. Moran [35] reported that women with PCOS had an elevated prevalence of impaired glucose tolerance (IGT), DM and MBS in both BMI and non-BMI-matched studies. Apridonidze., *et al*. [36] have also reported that MBS and its components were common with PCOS, increasing risk for CVD. Apridonidze., *et al*. [37] have reported MBS in 43% women with PCOS, nearly 2-fold higher than age-matched other women. Many years back Kidson [12] reported a 7-fold higher risk of myocardial infarction and ischemic heart disease in women with PCOS compared to the women of general population. Some studies revealed glucose intolerance present in as many as 40% of women with PCOS, when less stringent criteria were used [38]. In the study by Puurunen., *et al*. [17] serum hs-CRP levels were found to be increased in pre-and postmenopausal women with PCOS. Women with PCOS have anovulation but are not estrogen-deficient, enter menopause at a later age compared with normal women with higher risk of endometrial cancer. However epidemiological evidence to support this hypothesis is limited [36]. Many years ago, Swanson and colleagues [39] first reported the diagnostic criteria with vaginal ultrasound, characteristic enlarged stroma and many small follicles, looking like a string of pearls, on vaginal ultrasound. Significance of the necklace appearance of follicles is not clear. Most investigators believed that a minimum of 10 echo-free cysts of 2 - 8 mm in diameter must be present to diagnose PCOS. Balen., *et al*. [32] reported, ovarian morphology, as the most sensitive indicator. However. Fox [40] reported that 14 % of women who had Hirsutism, Oligomenorrhea, clinical and biochemical diagnosis of PCOS, did not have the increase in follicle numbers. It has been proposed that AMH could serve as an alternative to ovarian imaging, because its levels may be representative of follicle numbers with strong correlation between AMH and small antral follicle count. The fasting glucose insulin ratio (FGI) has become a very popular, accurate index of insulin levels, lower values depicting higher degree of IR and a ratio of less than 4.5 is predictive of IR [17]. The FGI was shown to be both sensitive and specific when PCOS cases were compared with normal controls. In hyperthecosis luteinized theca cells are found within the stroma distant from the follicles but in PCOS, these theca cells are present in the stroma immediately adjacent to follicles. However, several clinical features of hyperthecosis are also found in PCOS. So hyperthecosis could be a variant. Taylor [3] reported an elevated ratio of LH to FSH in approximately 40 - 70% of women with PCOS but LH/FSH ratio lacked sensitivity and specificity for diagnosis of PCOS. Shayya [41] reported that in PCOS, LH secretion was relatively insensitive to progesterone inhibition because of high levels of circulating androgens. Nagamani [42] reported normal immunoreactive LH levels but bioactive LH was markedly increased. Prolactin may also be elevated; while thyroid-stimulating hormone (TSH) is normal but coexisting thyroid disorder is possible. Infact the Rotterdam ESHRE/ASRM updated criteria for diagnosing PCOS after the exclusion of other etiologies, at least two of oligo- anovulation, hyperandrogenism and polycystic ovaries was driven by the awareness that PCOS was a syndrome with a broad spectrum of signs and symptoms of ovarian dysfunction. But these criteria are not the only problems in the syndrome. The concept that PCOS was heterogenous in clinical presentation and etiopathogenic mechanism was suggested by the National Institutes of Health workshop on PCOS in 2012. They recommended the use of the 2003 Rotterdam criteria but stressed the need to specify the PCOS

phenotype. They identified four phenotypes based on the actual presence of the diagnostic criteria, which showed how women affected by PCOS were not all equal. On that basis, clinical research on PCOS needed to take into account the heterogeneous etiology and clinical presentation of the syndrome. The results potentially affected by the actual composition of only study population.

Treatment challenges

Currently, PCOS has no cure. Variety of modalities are being used to treat and alleviate the symptoms of this enigmatic disorder with use of insulin-sensitizing agents, androgen-blocking medications, topical anti-hair growth, acne removal and keeping watch for diabetes CVD, and EC. Long-term follow-up is needed to determine the effectiveness of approaches in changing metabolic outcomes. Douglas., *et al*. [43] have shown that moderate reduction in dietary carbohydrates reduced the fasting and post-challenge insulin concentrations, which improved endocrine outcomes over the times. Insulin-sensitizing agents ameliorate IR and abnormalities in the endocrine, metabolic and reproductive systems. Metformin, a biguanide, has been extensively used with minimum risk of hypoglycemia. Pawelezyk., *et al*. [44] reported that Metformin not only restored normal levels of insulin and testosterone, but also decreased the pool of free, bioactive IGF-I by increasing the levels of circulating IGFBP-1. Wulffele., *et al*. [45] reported that Metformin decreased plasma triglycerides, cholesterol and LDL more than controls treatments with no effects on other outcomes. One other long-term study demonstrated a moderate improvement in plasma triglycerides. LDL cholesterol concentrations. Short-term administration had limited effects on women who had aberrant lipoprotein profiles at the outset. However, Yan [46] reported that the effect of Metformin on modulating lipoprotein profile was not convincing. A reduction of hyperinsulinemia has been associated with significant decrease in serum androgens, without a corresponding change in LH. Papunen., *et al.* [47] reported that regular menstruation and a measurable decline of Hirsutism occurred more often in women who look additional oral contraceptive pills than those who used only Metformin, Also, Harwood., *et al.* [48] have reported reduced hair growth in nearly two thirds of women due to decrease in ovarian and adrenal steroid production in Hirsute women. Anttilaa [49] reported depot and cyclical oral medroxyprogesterone (10 mg) suppressed pituitary gonadotropins and circulating androgens in women with PCOS. Administration of progesterone or OCP resulted in a greater suppression of mean LH and LH pulse frequency in normal women compared with women with PCOS. Eagleson [50] reported that an androgen-blocking agent prior to the administration of estrogen and progesterone, resulted in the restoration of LH pulse frequency in women with PCOS. Fedorcsak [25] reported women treated with insulin sensitizers, Diazoxide and Metformin had Leptin reduced, suggesting that improved insulin sensitivity and decreased circulating insulin levels diminished the insulin-mediated stimulation of leptin production among affected women. Walska., *et al*. [51] also reported that leptin, insulin growth factor 1 (IGF 1). Insulin-dependent proteins SHBG. Insulin-like growth factor-binding protein-1 (IGFBP-1). Insulin-sensitizing therapy could be considered as additional therapeutic option in obese women with PCOS. However, use has not been corroborated by other investigators. Antiandrogens such as spironolactone, cyproterone acetate (CPA), or flutamide were used. They acted by competitive inhibition of androgen-binding receptors or by decreasing androgen production.

Gonadotropins have the risk of hyperstimulation and require long courses at a considerable cost. The three LHRH agonists, D-Ser (Tbu) Glly LHRH ethylamine, (available nasal spray), D-Trp6-LHRH, administered by daily intramuscular injections and the long-acting preparation, D-Trp6 LHRH, (monthly intramuscular injection) are being used. They have similar efficacy in their ability to down regulate the pituitary-ovarian axis. The time required for the appearance of the suppressive effect is usually less than 14 days but never more than 18 days. Insler., *et al*. [52] reported the immunoreactive LH-reducing effect of the LH-RH agonists true only when the basic levels of the hormone, were higher than 11mlU/ml. Isolated ovarian surgery was considered in refractory cases, but may be it was as effective as no therapy in perimenopausal women.

Discussion

Not much is known about PCOS in later age. So, it continues to be more of a dilemma. Most clinicians find definitions confusing and difficult to explain. Variable presentations and controversial diagnostic criteria continue to hamper the diagnosis and management. Symp-

toms are so variable that it often goes undiagnosed for a long time. As knowledge of this complex, bit common syndrome is increasing, it has become obvious that these women are at risk of several health issues beyond their reproductive system and beyond reproductive life. Hyperandrogenemia/Hyperandrogenism are the key factors in disrupting ovarian physiology which is believed to be responsible for the typical clinical picture. Although PCO detected through ultrasound is a common feature of PCOS, it may not be present in all cases and may be present without PCOS, or with other disorders. So actually the name PCOS is a misnomer. Utility of AMH in adult/perimenopausal women has not been studied well.

Exact etiology of PCOS remains unknown. There are challenges not only to prevention, diagnosis but therapy too. Therapeutic interventions need to be directed towards addressing the individual needs and prevention of long-term complications. Azziz opened that the approach to PCOS in research and clinical practice needs to consider the heterogenicity of the disease and address differences between phenotypes, given the different roles of the diagnostic criteria. Research has to focus on the already defined phenotypes and even investigate the role of IR for diagnosis, treatment and prognosis given the importance of glucose metabolism. Lifestyle interventions are critical to the management of PCOS in adult and perimenopausal women. A healthy diet low in refined carbohydrates is important, to help regulate blood sugar levels. In postmenopausal women with PCOS information about glucose metabolism and androgen secretion is scarce. Regular exercise can also help the body regulate insulin and with healthy diet keep excess weight off regular. The management should include patient education. Special attention should be paid to the risk for diabetes, cardiovascular problems, obesity and endometrial cancer.

Conclusion

Etiology, diagnosis and management continue to be challenges in PCOS in adult and perimenopausal women and research needs to continue.

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