Volume 2 • Issue 2 • 2018

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Scientia Ricerca

Research Article

Gynaecology and Perinatology

ISSN: 2576-8301

Polycystic Ovarian Syndrome, a Multi Organ Disorder Not Just Ovarian

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Received: February 13, 2018; **Published:** May 16, 2018

Abstract

Polycystic ovarian syndrome is known since decades, but seems a misnomer, because of evidence of multisystem/multiorgan involvement. Symptoms vary. There is overproduction of ovarian androgens, luteinizing hormone may be others, causing hirsutism, menstrual irregularities, obesity, male-pattern balding, acanthosis negricans, sleep apnoea, polycystic ovaries, insulin resistance, hyperinsulinemia with hypertension, cardiovascular disease, diabetes mellitus, endometrial carcinoma risk. Some aspects are known, others need research, especially PCOS in adult, perimenopausal.

Information was collected by simple review from Google, Google Scholar, Bing, PubMed, Up-to-date, BMJ etc. personal experiences added. May be it is an autosomal dominant disorder with hypersensitive intra-ovarian-insulin-androgen signalling disturbance, hyperandrogenism, reduced insulin sensitivity. Hyperinsulinaemia stimulates lipid storage, alters triglycerides, low-density lipoproteins, cholesterol with sex hormone binding globulin elevated. Elevated serum leptin, insulin with obesity suggest linkage with each other. There is android obesity with waist-hip ratio > 0.8. Some believe that PCOS disappears around menopause, but not so, needs research. PCOS might persist or occur de novo at perimenopause is more difficult to diagnose, because menstrual abnormalities are common.

PCO, might not be present. Fasting glucose insulin ratio is popular diagnostic. Anti-Mullerian hormone which might be responsible for abnormalities has not been studied well. Etiology is not clear. Prevention has limitations, therapy, symptomatic, preventive not much known about oral contraceptive pills in perimenopausal women. Insulin-sensitizing agents can ameliorate IR, endocrine, metabolic abnormalities. Metformin does not increase insulin secretion or hypoglycaemia, seems safe. Education about prevention of obesity, diabetes, cardiovascular, endometrial cancer helps. Long-term follow-up is essential, with more research.

Keywords: *Misnomer; Polycystic Ovarian Syndrome; All Ages*

Volume 2 Issue 2 May 2018

Introduction

Gynaecological disorder, polycystic ovarian syndrome is known since decades. But it seems that it is a misnomer as it is not a disease simply with polycystic ovaries but involves many organs/systems and polycystic ovaries may not be there. The scope of this most common

endocrine disorder, has expanded from a gynaecological disorder to an endocrine–metabolic disorder that implies several consequences to the woman's health. This enigmatic entity seems to be affecting one in ten women. Quite a lot of information is available for PCOS in young women but not much of those who are near menopause. The symptoms are so variable that it often goes undiagnosed for a long time in adult/perimenopausal women.

Some researchers believe that PCOS disappears around menopause; however, this does not seem to be true, as symptoms and signs of PCOS linger years after the cessation of menstruation. Also it might occur de novo beyond young age. It is a systemic syndrome which affects more than one organ/system. The patients are at risk of serious conditions, other than reproductive dysfunction, depending upon organ/system most affected. Hirsutism, hair loss, weight gain, diabetes, hypertension, and endometrial cancer are not common in these women. As not much is known about PCOS in later age, it continues to be a bigger dilemma. Variable presentation and controversial diagnostic criteria continue to hamper the diagnosis and management.

Until now, the main focus in women with PCOS has been on infertility, anovulation and effects of hormonal disturbances during the reproductive period of life. However, as knowledge of this common but complex, syndrome is increasing, it is becoming obvious that these women are at risk of several heath issues beyond reproductive health and beyond the reproductive life. Studies demonstrate that the impairment of insulin sensitivity, impaired glucose metabolism, enhanced ovarian androgen secretion, and chronic inflammation observed in premenopausal women with PCOS persist after menopause, exposing them to Type 2 diabetes mellitus (T2DM). Cardiovascular disease (CVD) and metabolic syndrome (MBS). The time has come when the name should be changed.

Definition

PCOS, defined as per guidelines of proceedings of expert group includes (1) hyperandrogenism and/or hyperandrogenemia, (2) oligo-ovulation/anovulation after exclusion of (3) disorders known to cause similar symptoms and signs [1].

Some expert groups have 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) were sufficient for the diagnosis of PCOS.

This has expanded the NIH definition of 1990. There are two phenotypes

1. Ovulatory women with PCO and hyperandrogenism
2. Oligo-an ovulatory women with PCO without hyperandrogenism [2]. The second type may be more frequent in women beyond young age. Many women have PCO, but no PCOS and also there might be PCOS, but no PCO. So a lot of research is needed.

Incidence

PCOS affects 2 to 8% of population [3,4]. Azziz., *et al*. [5] studied 400 unselected consecutive premenopausal women (18-45 years of age) who reported for physical prior to employment and the cumulative presence of PCOS was 6.6% (26 of 400), including 15 subjects among the 347 women who completed evaluation and a calculated prevalence of 11.5 subjects among the remainder. Miller [6] reported the rates of PCOS in mothers and sisters of patients with PCOS as 24% and 32%, respectively, although the risk was higher when considering untreated premenopausal women only.

Etiopathology

As the exact cause of PCOS remains unknown, the disorder in adult and perimenopausal women is more difficult to understand. Genetic studies suggested an autosomal dominant transmission [7]. The interaction of a small number of key genes with environmental, particularly nutritional factors might be playing some role, causing the heterogeneity of clinical and biochemical features [8]. The results of the genetic analysis of several candidate genes and gene regions have suggested CYP11A (encoding cytochrome P450, family 11,

subfamily A polypeptides), CAPN10 (encoding calpain 10), the insulin gene VNTR (variable number of tandem repeats), and D19S884 (a dinucleotide repeat marker mapping to chromosome 19p13.2).

Past genetic studies related to PCOS have yielded only modest results but newer studies are likely to be rewarding for the genetic origin [9]. One study revealed that in women with oligomenorrhoea and hirsutism or hyperandrogenemia, family history of diabetes mellitus was present in 70%, hirsutism or menstrual disorders in 36 to 46% [10]. It might be hypersensitivity of the intra-ovarian-insulin-androgen-signalling pathway in families [11]. Dokras., *et al*. [12] reported that women with PCOS have an 11-fold higher prevalence of MBS compared with age-matched controls.

The condition appears to run in families, and sisters of those with disorder are twice likely to have it. It may be combination of environmental and genetic factors which favour the development of IR which leads to compensatory hyperinsulinemia, which substantially augments ovarian androgen synthesis by increasing luteinizing hormone (LH) pulse frequency at the pituitary level by stimulating gonadotropin-releasing hormone (GnRH), gene transcription in hypothalamic cells. 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 ovarian production of androgens may also worsen IR, precipitating a vicious cycle of IR – hyperinsulinemia – hyperandrogenemia [13]. Hyperinsulinaemia frequently stimulates lipid storage with altered lipoproteins, cholesterol levels with obvious hyperlipidaemia and obesity. Years back Franks [14] had reported that the IR present in 40-50% women with PCOS, played an important role in the dysregulation of folliculogenesis and the pathogenesis of the disorder, which was more marked in obese women, suggesting a synergistic effect. Also, obesity appeared to magnify all events by increasing androgen synthesis not only in ovaries, but also in subcutaneous adipose tissue and adrenal glands.

Androgens also triggered lipolysis, leading to elevated free fatty acids in circulation, favouring IR. However IR was not only in obese women, as lean women can also have IR. Kidson [15] reported that IR was not due to hyperandrogenism, because androgen blockade reduced IR only by 10-15%. Amelioration of hyperinsulinaemia was believed to result in a dramatic decline in circulating androgens. While many women with PCOS exhibited IR, not all did so [16]. However Conn [17] suggested that insulin may not play a major role in the pathophysiology of PCOS and hyperinsulinemia was probably an effect rather than cause in obese women. There was a link between elevated serum leptin/insulin and obesity in PCOS, which might be contributing to the complex nature of PCOS in obese patients [18].

Puurunen., *et al*. [19], reported that women with PCOS exhibited higher insulin levels as well as increased insulin responses in OGTT before and after menopause, indicating a greater degree of IR than in the control women. Similarly, they had increased HOMA-IR values, compared with control women. Furthermore, the whole-body insulin sensitivity index (ISI), described by Matsuda and DeFronzo [20] was found to be decreased in pre- and postmenopausal women with PCOS, similar to previous studies indicating that premenopausal women with PCOS more often have altered glucose metabolism, exhibited by increased IR and more frequent occurrence of T2DM compared with healthy women [21,22].

Shaw., *et al*. [23] found that women who reported irregular menstruation and biochemical evidence of hyperandrogenism had more IR and more often had T2DM compared with controls. In postmenopausal women with PCOS data on glucose metabolism and androgen secretion is scarce. Puurunen., *et al*. [19] reported that impaired glucose metabolism, enhanced ovarian androgen secretion, and chronic inflammation observed in premenopausal women with PCOS persisted after menopausal transition which emphasised life-long health risks. IR is related to the action, but hyperinsulinemia, is circulating insulin, a characteristic independent of obesity, though obesity does aggravate pre-existing IR.

The mechanism by which obesity caused IR was unclear, though a post receptor defective insulin receptor signalling was suggested [24]. Legro., *et al*. [25] reported that hyperinsulinaemia increased ovarian androgen production by stimulating an ovarian enzyme, cytochrome P450c17a, 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, increasing the bioavailability of androgens, with increase in bound and unbound testosterone [26]. Puurunen., *et al*. [19] reported that decreased ovarian capacity to secrete 17-OHP after menopause in the pre-and post-menopausal women, was significantly enhanced in women with PCOS.

This supported the results of a previous study [66] by the researchers which had revealed that both pre-and postmenopausal women with PCOS exhibited increased adrenal androgen secretion capacity. In comparison with controls, the women with PCOS participating in the study had lower SHBG levels before and after menopause. In controls, serum SHBG levels decreased and subsequently free androgen index (FAI) increased, but the values remained significantly lower than in the women with PCOS, whose SHBG levels remained low and unchanged after menopause. Moreover, the elevated androgen to estrogen ratios in women with PCOS pre-and postmenopausal supported the fact that a hyperandrogenic milieu persisted beyond menopause.

The impact of hyperandrogenism in the postmenopausal period is not well understood, but the results of a recent study indicated that low circulating level of SHBG was a strong predictor of the risk of T2 DM [27]. Furthermore, the results of another study suggested that high serum testosterone levels in postmenopausal women were associated with an increased risk of CVD, but whether or not testosterone played a role as a marker or mediator in the process needed further investigations [28]. Azziz., *et al*. [29] and Goodarzi [30] have also suggested that these women exhibited overproduction of ovarian androgens, increased pituitary LH secretion, incomplete maturation of ovarian follicles, IR, and hyperinsulinemia.

Leptin, an appetite-suppressing hormone produced in fat tissue 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 [31,32]. Some researchers reported that leptin levels were higher in PCOS [33], others reported, levels similar to those in weight-matched controls [34-36]. Caro [37] also reported the mean value of leptin not different in women with PCOS compared to normal women. Fedorcsak [38] found no significant difference between leptin levels of women with PCOS and controls, independent of obesity.

However leptin deficiency and PCOS appeared to have many similarities between their clinical, metabolic and biochemical features and more research is needed. Spritzer [39] reported that Insulin and leptin levels correlated well, suggesting that insulin and leptin resistance could co-occur. El-Gharib [18] reported reduced Leptin levels in women with PCOS treated with insulin sensitizers which suggested that the improved insulin sensitivity with the associated decrease in the circulating insulin levels diminished the insulin-mediated stimulation of leptin production among these women. Leptin lead to a chronic systemic inflammatory state which seemed to be a feature of PCOS also.

Reduction in 17a-hydroxyprogesterone in response to challenges with GnRH, HCG, and ACTH following short-term metformin therapy in obese and lean women with PCOS have suggested that the reduction in ovarian and adrenal cytochrome p45017a–enzyme activity may be responsible for the amelioration of hyperandrongenaemia in these women [40]. Moreover, androgens seemed to diminish highly oxidative and insulin-sensitive Type I Muscle fibres (TIMF) and increase glycolytic and less insulin-sensitive Type II muscle fibres (TIIMF), further favouring the development of IR [41-43].

The degree to which the hormonal and metabolic alterations persist after menopause is not well documented. Elevated levels of inflammatory markers reflect impaired carbohydrate and lipid metabolism, chronic inflammation, which add to the risk of CVD [44,45]. Normally, during menopausal transition, several hormonal and metabolic changes take place. Androgen levels are known to remain stable or even rise and also estrogen levels decrease dramatically [46, 47]. However IR, chronic inflammation, abdominal adiposity, and dyslipidemia tend to worsen in women with PCOS, as they become more androgenic [48-52].

There is clear evidence that women with PCOS are at 3 to 7 times increased risk of developing T2 DM and CVD [53-57], evidence of dyslipidaemia [58-61] and abnormal vascular function [62-64]. However Wild., *et al*. [65] reported no direct evidence of increase in CVD events in middle-aged women with a history of PCOS, although the incidence of stroke was slightly increased. So again the question is follow up of women with PCOS during adolescence and possibilities of denovo PCOS at later ages. In a recent study in women with PCOS, adrenal androgen secretion was found to remain pronounced up to menopause, which indicated that exposure to hyperandrogenism persisted for a long time in these women [66].

It seems possible that long-lasting hyperandrogenism may magnify the unfavourable hormonal and metabolic changes related to menopause and expose these women to increased health risks. In a study glucose tolerance, ovarian steroid production capacity, and chronic inflammation were studied in pre- and postmenopausal women with PCOS by means of oral glucose tolerance tests (OGTT), human chorionic gonadotropin (HCG) tests, and assay of high-sensitivity C-reactive protein (hs-CRP). Studies have suggested that anti-Mullerian hormone (AMH) might in part be responsible for the increased follicles in the ovary. AMH, produced by the granulosa cells of growing pre-antral and small antral follicles, appears to negatively regulate the advancement of follicle maturation [67]. Women with PCOS have two to three fold higher circulating AMH levels compared to normal cases. This could be reflective of more growing pre-antral and small antral follicles, leading to PCO [68]. Not much is known about this, in adult and perimenopausal women. Studies are needed.

Clinical Features

While young women with PCOS presented with infertility, hirsuitism, acne with anovulation and PCO, major clinical features of PCOS in adult and perimenopausal women are menstrual irregularities, PCO, commonly accompanied by obesity. Because of hyperandrogenism and IR, the obesity in PCOS is of android (central) type with a waist-hip ratio of > 0.8 [69]. Taylor [3] reported obesity, in 35 to 50% women with PCOS. Other features are male-pattern balding, acanthosis negricans (darkened, thickened skin around the neck, armpits, or breasts), sleep apnea, hypertension, DM, endometrial carcinoma, and CVD [70].

Balen., *et al*. [71] reported hirsutism in 70% but Taylor [3] reported less common frequency with gradual onset. In two large studies, the prevalence of hirsutism was 56 to 58% and 70 to 73% among normal weight and obese women respectively. Conway and colleagues [72] found alopecia in 8% and hirsutism of various degrees in 61% cases with PCO identified by ultrasound. Taponen., *et al*. [73] reported PCO in 37.3% women with self-reported symptoms of oligomenorrhoea and hirsutism compared to 18.2% amongst controls. Only 12 to 22% of obese women with PCO by ultrasound described regular menstrual cycles, compared to 28 to 32% of normal weight women. Acne has been reported in 25 to 35% patients [71].

Actually perimenopausal women with PCOS often have features similar to the features of MBS or "syndrome X" hyperlipidaemia, hypertension, T2 DM, or impaired glucose. The MBS and its individual components are common in PCOS, particularly among women with the highest insulin levels and BMI. Hyperinsulinemia seems to be a common pathogenetic factor for both PCOS as well as MBS [74]. Moran [75] reported that women with PCOS had an elevated prevalence of IGT, DM and MBS in both BMI and non-BMI-matched studies. Apridonidze., *et al*. [76] have also reported that the MBS and its components were common in women with PCOS, with increased risk for CVD. Women with PCOS and the MBS differ from those without MBS in terms of increased hyperandrogenemia, lower serum SHBG, and higher prevalence of acanthosis nigricans, all features that may reflect severe IR.

Apridonidze., *et al.* [77] have reported the prevalence of MBS in 43% cases with PCOS, nearly 2-fold higher than in age-matched women of the general population. Women with both MBS and PCOS are more hyperandrogenic and have lower levels of SHBG than those with PCOS alone. The relatively severe hyperandrogenemia, acanthosis negricans, low serum SHBG found in women having both PCOS and MBS reflected IR of increased severity. Kidson [15] many years back 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 in as many as 40% cases of PCOS, when less stringent WHO criteria were used [25].

Atherosclerosis is considered to be associated with chronic inflammation. Serum levels of hs-CRP reflected the inflammatory milieu and have been shown to correlate well with the risk of CVD and related events [45]. In the study by Puurunen., *et al*. [19], serum hs-CRP levels were increased both in pre- and postmenopausal women with PCOS compared to controls. Shaw., *et al*. [78] reported increased serum hs-CRP levels in women with PCOS after menopause. Women with PCOS are not estrogen-deficient, despite their anovulation, enter menopause at a later age, compared with normal women. So they are at increased risk for endometrial cancer with chronic anovulation with unopposed estrogen exposure of the endometrium, though epidemiological evidence to support this hypothesis is limited [79]. Because of an increased risk of endometrial cancer, women with PCOS undergo hysterectomy more often.

Diagnosis

Apart from core diagnostic criteria of hyperandrogenism and menstrual dysfunction, a host of clinical, pathological, and biochemical abnormalities coexist with PCOS. These are not essential for the diagnosis. Three different statements on diagnostic criteria have been described in the literature most clinicians find these different definitions confusing and difficult to explain to the patients. As there are differences in criteria used by various studies, standardization is difficult (Table 1).

NIH Statement [80] Includes all the following: 1. Hyperandrogenism and/or hyperandrogenemia 2. Oligo-ovulation 3. Exclusion of related disorders[a]
ESHRE/ASRM Statement [81] Includes two of the following, in addition to exclusion of related disordersa. 1. Oligo-ovulation or anovulation (e.g., amenorrhoea, irregular uterine bleeding) 2. Clinical and/or biochemical signs of hyperandrogenism (e.g., hirsutism, elevated 3. serum total or free testosterone) 4. Polycystic ovaries (by ultrasonography) polycystic ovary having 12 or more follicles, measuring between 2 and 9 mm, and/or an ovarian volume > 10 cc. Androgen Excess Society (AES) suggested criteria for the diagnosis of PCOS1 Includes all of the following: 1. Hyperandrogenism: hirsutism and/or hyperandrogenemia 2. Ovarian dysfunction: oligo-ovulation and/or polycystic ovaries 3. Exclusion of other androgen excess or related disordersa

Table1: *Diagnostic Parameters.*

Related disorders to be excluded: 21-hydroxylase-deficient non-classic adrenal hyperplasia thyroid dysfunction, hyperprolactinemia, neoplastic androgen secretion drug-induced androgen excess, the syndromes of severe insulin resistance, Cushing's syndrome, and glucocorticoid resistance. NIH National institutes of health, ESHRE European Society for Human Reproduction and Embryology, ASRM American Society for Reproductive Medicine, AES Androgen Excess Society [82].

Because of the drop in estrogen and altered progesterone levels that accompany menopause, monitoring is based upon blood testosterone and dehydroepiandrosterone sulfate (DHEA-S). Swanson and colleagues [83] were the first to report the diagnostic criteria of characteristic enlarged stroma and many small follicles in the ovaries often looking like a string of pearls, on vaginal ultrasound. Significance of this 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 in ovaries to diagnose PCOS [84].

Balen., *et al.* [71] reported, ovarian morphology the most sensitive indicator. However, Fox [85] reported that 14% of women who had hirsutism, oligomenorrhoea with clinical and biochemical diagnosis of PCOS, did not have the described increase in follicle numbers visible on ultrasound. Although PCO detected through ultrasound is a common feature of PCOS, it may not be present in PCOS and may be present with no PCOS. PCO may also be present in women with other disorders. So ideally the name PCOS needs to be changed.

It has been further proposed that AMH could serve as an alternative to ovarian imaging because its levels may be representative of follicle numbers per ovary based on the strong correlation between serum AMH and small antral follicles [86]. The fasting glucose insulin ratio (FGI), described by Lergo [50] has become a popular, accurate index of insulin levels, lower values depicting higher degrees of IR and a ratio of less than 4.5 is predictive of IR. The FGI has been shown to be both sensitive (95%) and specific (84%) when PCOS cases were compared with normal controls [87].

Ehrmann., *et al.* [74] reported significantly higher fasting insulin levels in women with PCOS than normal women. Approximately 60-80% of women with PCOS demonstrated elevated circulating androgen levels. Biochemical hyperandrogenemia prevails in 40% of women with PCOS. Some have reported hyperandrogenism central to the diagnosis with higher testosterone than nonhirsute women with normal cycles or women with ovulatory dysfunction of other causes [10].

Hyperthecosis is a pathologic diagnosis in which luteinized theca cells are found within the stroma distant from the follicles. In PCOS, these theca cells are present in the stroma immediately adjacent to follicles. Several clinical features of hyperthecosis are also found in PCOS. So it could be a variant [88]. El-Gharib [18] have reported that salivary levels of LH, free testosterone and Dehydroepiandrosterone Sulfate (DHEA-S) correlated with corresponding serum values. Saliva had a higher sensitivity than serum and provided a sensitive, simple, reliable, non-invasive and uncomplicated diagnostic approach for biochemical hyperandrogenemia.

Taylor [3] reported an elevated ratio of LH to FSH in approximately 40-70% of women, but LH/FSH ratio lacked sensitivity and specificity for diagnosis of PCOS. Shayya [89] reported that in PCOS, LH secretion was relatively insensitive to progesterone inhibition because of high levels of circulating androgens. Nagamani [90] reported immunoreactive LH levels normal, bioactive LH was markedly increased. Prolactin may also be elevated, while thyroid-stimulating hormone (TSH) is normal.

Management

Etiology of PCOS is not clear, specially not much is known specially about PCOS in perimenopausal women. So there is limitation not only to prevention but therapy also. Currently, PCOS has no cure, but a variety of treatments are used to alleviate the symptoms and signs of this enigmatic disorder. Therapeutic interventions are directed towards addressing the individual needs and prevention of long-term complications. Management in adult/perimenopausal women depends on women's degree of hirsutism, obesity and other symptoms as well as signs and is primarily directed towards alleviating symptoms and manifestations.

Use of insulin-sensitizing medications, androgen-blocking medications, topical anti-hair-growth medications, other excess hair treatments, treatments for hair loss, acne treatments, removal of other skin problems and keeping watch for risk of diabetes and CVD. Long-term follow-up is needed to determine the effectiveness of approaches in changing metabolic outcomes without causing harm. Douglas., *et al*. [91] have shown that moderate reduction in dietary carbohydrates reduced the fasting and post-challenge insulin concentrations, which over the time improved endocrine outcomes. Insulin-sensitizing agents ameliorated IR and abnormalities in the endocrine, metabolic and reproductive systems. Metformin, a biguanide, has been extensively used.

The action of metformin is not associated with an increase in insulin secretion, and there is no risk of hypoglycaemia. Pawelczyk., *et al*. [92] 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*. [93] reported that metformin decreased plasma triglycerides, cholesterol and LDL more than control treatments, with no effect on other outcomes. Short-term administration had limited effects on women who had aberrant lipoprotein profiles at the outset.

But Yen [88] reported that the effect of metformin on modulating lipoprotein profile was not convincing. A reduction of hyperinsulinemia has been associated with significant decrease of serum androgens, without a corresponding change in LH, in women treated with insulin-lowering drugs, and this suggested a role for insulin in LH-stimulated androgen synthesis. Prevention of diabetes, MBS, and endometrial carcinoma is essential by treating detected abnormalities in various systems. Papunen., *et al*. [94] reported that regular menstruation and a measurable decline of hirsutism occurred more often in women who took OCPs also than those who used only metformin. Morreale [95], Batakun [96], Batalun [97], Harwood [98] have reported reduced hair growth in nearly two thirds of women by decreasing ovarian and adrenal steroid production in hirsute women.

Anttila [99] 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 [100,101]. Eagleson [102] 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 [38] reported women treated with the insulin sensitizers, Diazoxide and metformin had reduced Leptin levels, suggesting that improved insulin sensitivity and decreased circulating insulin levels diminished the insulin-mediated stimulation of leptin production among affected women.

Kowalska., *et al*. [103] also reported leptin, insulin growth factor I (IGF-I), insulin-dependent proteins SHBG, insulin-like growth factor-binding protein-1 (IGFBP-1), Insulin-sensitizing therapy could be considered a therapeutic options in obese women with PCOS. However, this has not been corroborated by other investigators [104,105]. Antiandrogens such as spironolactone, cyproterone acetate (CPA), or flutamide were used and acted by competitive inhibition of androgen-binding receptors or by decreasing androgen production [106].

Gonadotropins have the risk of hyperstimulation and require long courses of therapy at a considerable cost. The three LHRH agonists, D-Ser (tBU) Gly LHRH ethylamide, (comes in the form of a nasal spray), D-Trp6-LHRH, (administered by daily intramuscular injections) and the long-acting preparation, D Trp6 LHRH, (given monthly intramuscular injection) are being used. They have similar efficacy down regulating the pituitary-ovarian axis [107]. The time required for the appearance of the suppressive effect is usually less than 14 days but never more than 28 days. Insler., *et al*. [107] reported the immunoreactive LH-reducing effect of the LH-RH agonists true only if the basic levels of the hormone were higher than 11 mlU/ml. isolated ovarian surgery was considered in refractory cases, but was found to be as effective as no therapy in perimenopausal women!

Lifestyle interventions are critical to the management of PCOS in adult and perimenopausal women. Screening for depression and anxiety with appropriate psychological instruments are essential. Management is age and need oriented, crux being lifestyle changes, diet, exercises, OCPs, Insulin sensitizers and progesterone for bleeding. Statins, anti-diabetics and anti-hypertensives are used as per the need. Omega-3 Fatty acids and micronutrients (inositol and micro inositol) or N-Acetylcysteine are alternative medicines. Diet low in refined carbohydrates helps in regulating blood sugar levels. Exercises can also help the body regulate insulin and keep excess weight off. Control in weight with healthy diet and regular exercises on a day-to-day basis are essential.

Losing weight is challenging with PCOS but can help in many ways including help reduce the male hormone levels in the body. With a proper diagnosis, lifestyle changes and PCOS treatment, women can get a lot of relief from the overwhelming health problems [108]. The weight loss that often accompanied protracted therapy may account for some of the beneficial effects. Because of no estrogen from the ovaries, the body has to rely on fat and the adrenal glands for hormone production. Even moderate weight loss in obese subjects can result in improved insulin sensitivity, reduction of hyperandrogenism, hirsutism and improved menstrual function, so it should be the first line of management in obese patients.

A post-menopausal woman with PCOS needs to follow a strict exercise regimen and follow a diet that is lower in carbohydrates. Cigarette smoking should be strongly discouraged as it exacerbated the already increased risk of atherosclerosis. Many organs/systems are

affected. Prospective studies with adequate study populations and follow-up about PCOS in peri/post-menopausal women are needed [109-113].

Conclusion

The scope of the most common endocrine disorder PCOS, has expanded from a gynaecological disorder to an endocrine–metabolic disorder that implies several consequences to the woman's health. These women are at risk of several heath issues beyond their reproductive years. Studies have demonstrated that the impaired glucose metabolism, enhanced ovarian androgen secretion, and chronic inflammation are the main issues. The impairment of insulin sensitivity, hyperandrogenism, and chronic inflammation, persist in these women with PCOS, exposing them to T2DM, MBS, and CVD. There is a link between elevated serum leptin and insulin to obesity in PCOS.

Apart from core diagnostic criteria of hyperandrogenism and menstrual dysfunction, a host of clinical, pathological, and biochemical abnormalities coexist with PCOS. There is limitation not only to prevention but therapy also. Currently, PCOS has no cure, but a variety of treatments are used to alleviate the symptoms. Lifestyle interventions are critical to the management of PCOS in adult and perimenopausal women. A healthy diet low in refined carbohydrates is important, as this can help regulate blood sugar levels. Exercise can also help the body regulate insulin and keep excess weight off. Control in weight with healthy diet and regular exercises on an everyday basis are essential. The management should include patient education. Special attention should be paid to the risk for diabetes, cardiovascular problems, obesity and endometrial cancer.

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