

Polycystic ovarian disease in adult and perimenopausal women

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Abstract

Polycystic ovarian disease (PCOD) is most common endocrine disorder in women. Symptoms are variable and often involve more than one body function. The major clinical features are hirsutism, menstrual irregularities, obesity, insulin resistance, hyperinsulinemia, polycystic ovaries (PCO). Other characteristics include male-pattern balding, acanthosis nigricans, sleep apnea with increased risk for hypertension, cardiovascular disease, diabetes mellitus, endometrial carcinoma, and overproduction of ovarian androgens and luteinizing hormone. While some believe that PCOD disappears after menopause, symptoms can persist after menopause. The cause of PCOD is still unknown. Genetic studies suggest that transmission is autosomal dominant with decreased penetrance because of hypersensitive intra-ovarian-insulin-androgen signaling with disturbances in gonadotropin levels, hyperandrogenism, and reduced insulin sensitivity. Hyperinsulinaemia frequently stimulates lipid storage with alterations in lipoproteins, cholesterol, hyperlipidaemia obesity. Anti-Mullerian hormone might be responsible for these abnormalities.

Information on PCOD in adult perimenopausal women is scarce as it may be difficult to diagnose, since one marker is irregular menstruation. PCO, a common feature of PCOD, may occur with or without other disorders and the associated obesity is of android (central) type with a waist-hip ratio (WHR) of > 0.8. Fasting glucose insulin ratio (FGI) has become a popular diagnostic criteria. Triglycerides, low-density lipoprotein (LDL), and cholesterol are elevated with decreased levels of sex hormone binding globulin (SHBG) due to hyperinsulinemia. The elevated levels of serum leptin and insulin and their linkage to obesity suggest the potentially complicated implications for obese patients.

Preventative measures for PCOD are limited. Clinical management is primarily focused on treating symptoms and manifestations and preventing long-term complications. Oral contraceptive pills (OCP) have several benefits, including treatment of irregular menstruation. Insulin-sensitizing agents can ameliorate insulin resistance, endocrine, and metabolic reproductive abnormalities. Metformin has been extensively used and is not associated with an increase in insulin secretion or risk of hypoglycaemia. The weight loss that accompanies protracted therapy may account for some of the beneficial effects. Long-term follow-up is needed to determine the effectiveness in changing the metabolic outcomes without causing other complications, such as reducing hair growth. Management should include patient education, with particular attention to diabetes, cardiovascular risk, obesity and endometrial cancer.

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Background

Polycystic ovarian disease (PCOD) is the most common endocrine disorder in women, as many as one in ten women may be living with it. The symptoms are so variable that it often goes undiagnosed for a long time. Polycystic ovarian syndrome (PCOS), as was called and, described by Stein and Levantahl in the middle 1900s, is known to cause hyperandrogenism with ovulatory dysfunction and can occur any time between adolescence to menopause with sequale [1, 2]. However PCOD is a systemic syndrome, affects more than one body function, and the patients are at risk of other serious conditions. Some believe that PCOD disappears after menopause; however, this is an incorrect assumption, as symptoms can linger for many years after the cessation of menstruation. Hirsutism, hair loss, and weight gain often continue and diseases such as diabetes, hypertension, and endometrial cancer become evident. However, not much is known about PCOD in adult and perimenopausal women, so it continues to be a dilemma. Variable presentation and controversial diagnostic criteria continue to hamper its diagnosis and understanding. The present article is to update and disseminate information about this disorder.

PCOD, as defined as per the guidelines of the proceedings of an expert group conference sponsored by the National Institutes of Health (NIH) in April 1990, is a disorder with (1) hyperandrogenism and/or hyperandrogenemia, (2) oligo-ovulation and (3) exclusion of disorders known to cause similar symptoms and signs [3]. However, another expert group conference held in Rotterdam in May 2003 suggested that having two out of the three features are sufficient for a PCOD diagnosis: (1) oligo- or anovulation (2) clinical and/or biochemical signs of hyperandrogenism and (3) polycystic ovaries (PCO), excluding other disorders which can cause these problems. This expanded the NIH definition of 1990, creating two new phenotypes (1) ovulatory women with PCO and hyperandrogenism or (2) oligo-anovulatory women with PCO without hyperandrogenism [4, 5].

Incidence

It has been reported that PCOD affects 2 to 8% of population [6, 7].

Etiopathology

The exact cause of PCOD remains unknown. Genetic studies suggest an autosomal dominant transmission with decreased penetrance [8]. One study revealed that approximately 70% women with oligomenorrhoea and hirsutism or hyperandrogenemia have a family history of diabetes mellitus and 36 to 46% have family history of hirsutism or menstrual disorders [9]. PCOD may occur due to hypersensitivity of the intra-ovarian-insulin-androgen-signaling pathway. A comprehensive characterization of this potential defective signaling could have significant implications for the development of more specific and efficient treatment plans [10]. In adult PCOD, the basis for chronic anovulation has been in part attributed to lack of follicle-stimulating hormone (FSH) or FSH bioactivity [11].

Recent studies have suggested that anti-Mullerian hormone (AMH) might in part be responsible for the increased follicle population in PCO. AMH, produced by the granulosa cells of growing pre-antral and small antral follicles, appears to negatively regulate the advancement of follicle maturation [12]. Women with PCOD have two- to three-fold higher circulating AMH levels compared to normal cases. However, this could be reflective of the increased numbers of growing pre-antral and small antral follicles, which may lead to PCO [13].

Although the exact pathophysiology is not known, disturbances in gonadotropins and reduced insulin sensitivity are known to contribute to the overproduction of androgens. Hyperinsulinaemia frequently stimulates lipid storage with altered lipoprotein and cholesterol levels with obvious hyperlipidaemia and obesity. Several years ago, Franks [14] had reported that the insulin resistance present in approximately 40-50% of cases plays an important role in both the dysregulation of folliculogenesis and the pathogenesis of the disorder, which is more marked in obese patients, suggesting a synergistic effect. Hyperinsulinaemia is usually not

present. Others have suggested that evaluation of insulin resistance rather than a single insulin value may be more sensitive indicator [15]. Furthermore insulin resistance is not exclusive to obese women, as lean women can also be insulin resistant nor is it due to hyperandrogenism, because androgen blockade reduces insulin resistance only by 10-15% [16]. Amelioration of hyperinsulinaemia is believed to result in a dramatic decline of circulating androgens. While many women with PCOD exhibit insulin resistance, not all do. This feature of the disease is not present in all patients [17]. The mechanism through which obesity causes insulin resistance is unclear, though a post receptor defective insulin receptor signaling has been suggested [18]. Defective glucose transport as a consequence of reduced glucose transporter protein 4 (GLUT – 4) production has been reported as a cause of general insulin resistance, and in particular, for PCOD [19]. Legro et al [15] report that hyperinsulinaemia increases ovarian androgen production by stimulating an ovarian enzyme complex, cytochrome P450c17a, either directly or via luteinizing hormone (LH) secretion. Insulin may potentiate the action of adrenocorticotrophic hormone (ACTH) on adrenal steroidogenesis and contribute to hyperandrogenism through its inhibitory effect on hepatic sex hormone binding globulin (SHBG) production, thereby increasing the bioavailability of androgens, with increase in bound and unbound testosterone [20]. Conn [21] suggests that insulin may not play a major role in the pathophysiology of the PCOD and increased insulin is probably an effect rather than causative in obese PCOD patients.

Clinical features

Major clinical features of PCOD are hirsutism as a result of hyperandrogenism, which also causes menstrual irregularities, PCO, and is commonly accompanied by obesity and insulin resistance. Other symptoms include: male-pattern balding, acanthosis nigricans (darkened, thickened skin around the neck, armpits, or breasts) and sleep apnea. Women with PCOD are at increased risk for hypertension, diabetes mellitus, endometrial carcinoma, and cardiovascular disease. Furthermore, they may exhibit other clinical traits including the overproduction of ovarian androgens, increased pituitary luteinizing hormone

(LH) secretion, incomplete maturation of ovarian follicles, insulin resistance, and hyperinsulinemia. [22, 23].

Balen *et al.* [24] reported that as many as 70% women with PCOD have hirsutism but Taylor [6] reported that virilization is uncommon and always gradual in onset. Conway and colleagues [25] identified alopecia in 8% and hirsutism of various degrees in 61% of female patients with PCO identified by ultrasound. In two large studies, the prevalence of hirsutism was 56 to 58% and 70 to 73% among normal weight and obese PCOD patients, respectively. Taponen *et al.* [26] reported PCO in 37.3% of women with self-reported symptoms of oligomenorrhoea and hirsutism compared to 18.2% controls. Only 12 to 22% of obese women described regular menstrual cycles, compared to 28 to 32% of normal weight women diagnosed with PCO by ultrasound. Acne has been described in 25 to 35% patients [24]. Obesity, is found in 35 to 50% [6].

Perimenopausal women with PCOD often have hyperlipidaemia, hypertension, type 2 diabetes mellitus, or impaired glucose tolerance similar to the features of “metabolic syndrome” (MBS) or “syndrome X” [16]. Apridonidze *et al.* [27] have reported the prevalence of MBS in women with PCOD as 43%, nearly 2-fold higher than in age-matched women in the general population. Women with both MBS and PCOD are more hyperandrogenic than those with PCOD alone and have lower levels of SHBG. The relatively severe hyperandrogenemia, increased prevalence of acanthosis nigricans, and low serum SHBG found in women having both PCOD and MBS may reflect insulin resistance of increased severity in these patients [27]. Kidson [16] also report that there is a 7-fold higher risk of myocardial infarction and ischaemic heart disease compared to the general population of women. The prevalence rate of PCOD is 10% and therefore the relative risk of premature ischemic heart disease in these cases of PCOD appears to be 7%. Women with PCOD are not estrogen-deficient, and despite their anovulation, enter menopause later as compared with normal women. However, they have an increased risk of endometrial cancer, therefore more often undergo hysterectomy.

Diagnosis

Information about PCOS in adult perimenopausal women is scarce. It may be difficult to diagnose and monitor during this period, given that one of the markers is irregular menstruation, which is also a feature of perimenopause. Once a woman goes through menopause, she can no longer be used to indicate reproductive system problems. Because of the drop in estrogen and altered progesterone levels that accompany menopause, diagnosing and monitoring PCOD based upon blood measurements of testosterone and dehydroepiandrosterone sulfate (DHEA-S).

Many years ago, Swanson and colleagues [28] had first reported the diagnosis of PCOD with its characteristic enlarged stroma and many small follicles, often looking like a string of pearls, by vaginal ultrasound. Significance of this necklace appearance of follicles is not clear. Most investigators believe that a minimum of 10 echo-free cysts of 2-8 mm in diameter must be present to diagnose PCOD [29]. However, Fox [30] reported that 14% of women who had hirsutism and oligomenorrhoea and further clinical and biochemical diagnosis of PCOD did not have the described increase in follicle numbers as seen as ultrasound. As such PCO detected through ultrasound is a common feature of women with PCOD, but may also occur in women with or without other disorders [31]. Conversely, PCO may not be present in women with PCOD. It has been proposed that AMH could serve as an alternative to ovarian imaging because its levels may be representative of follicle number per ovary based on the strong correlation between serum AMH values and small antral follicle count [32]. Balen *et al.* [24] believe that ovarian morphology may be the most sensitive indicator of PCOD. Some studies have revealed that glucose intolerance is present in as many as 40% of women with PCOD when less stringent WHO criteria are used [15].

Because of hyperandrogenism and insulin resistance, the obesity in PCOD is of android (central) type with a waist-hip ratio of > 0.8 [33] accompanied by an increased risk of diabetes mellitus and cardiovascular disease [34]. The fasting glucose insulin ratio (FGI), described in 1998, has become a very popular, accurate index of insulin levels with lower values

depicting higher degrees of insulin resistance determined by calculating the FGI, and a ratio of less than 4.5 is predictive of insulin resistance [15]. The FGI has been shown to be both sensitive (95%) and specific (84%) compared with controls [35]. Ehrmann *et al.* [36] and El – Gharib *et al.* [37] report significant higher fasting insulin levels in women with PCOD than normal controls. Approximately 60-80% of women with PCOD demonstrate elevated circulating androgen levels. Biochemical hyperandrogenemia prevails in 40% of women with PCOD. Hyperandrogenism is central to the diagnosis with higher testosterone than nonhirsute women with normal cycles or women with ovulatory dysfunction of other causes [9].

Leptin, an appetite-suppressing hormone produced in fat tissue that plays a significant role in the regulation of body fat mass [38, 39], has been reported to be higher in PCOD [40, 41] but similar to those in weight-matched controls by others [42] [43]. Caro [44] reported that the mean value of leptin was not different in women with PCOD compared to normal women. Fedorcsak [45] found that independent of obesity, leptin levels do not differ significantly between PCOD and controls. Leptin deficiency and PCOD appear to have many similarities between their clinical, metabolic and biochemical features. Insulin and leptin levels are positively correlated, suggesting that insulin and leptin resistance could co-occur [46]. El-Gharib [37] reported that Leptin levels were reduced in women with PCOD who were treated with the insulin sensitizers (Diazoxide and metformin), suggesting that the improved insulin sensitivity with the associated decrease in circulating insulin levels diminish the insulin-mediated stimulation of leptin production among these women. Conversely, there are reports that, leptin levels do not differ significantly between women with PCOD and controls, when considered independently from obesity. Significant positive correlation between age, BMI, and leptin, and a small, but insignificant, positive correlation between leptin and insulin have been reported. There is a link between elevated serum leptin and insulin levels to obesity in PCOD, suggesting that these factors contribute to the complex nature of complicated picture of PCOD in obese patients [37].

Hyperthecosis is a pathologic diagnosis in which luteinized theca cells are found within the stroma

distant from follicles. In PCOD, these theca cells are present in the stroma immediately adjacent to follicles. Several clinical features of hyperthecosis are also found in PCOD, so it could be a variant [47]. El-Gharib [37] report that salivary levels of LH, FT and DHEA-S correlate with their corresponding serum values. Saliva has a higher sensitivity than serum and provides a sensitive, simple, reliable, non-invasive and uncomplicated diagnostic approach for biochemical hyperandrogenemia. Taylor [6] has reported an elevated ratio of LH to FSH in approximately 40 - 70% of women, but rate of LH/FSH lacks sensitivity and specificity for diagnosis of PCOD. Nagamani [48] report that although immunoreactive LH levels are normal, bioactive LH is markedly increased. Prolactin may also be elevated, while thyroid-stimulating hormone (TSH) is normal.

The diagnosis of insulin resistance is made by determining the FGI ratio. A ratio of less than 4.5 is indicative of insulin resistance [15]. Triglycerides, low density lipoprotein (LDL), and cholesterol are elevated with decreased levels of SHBG due to hyperinsulinemia [9, 14]. Insulin resistance which relates its action but hyperinsulinemia which is related to circulating insulin is a characteristic of PCOD and is independent of obesity, though obesity does aggravate pre-existing insulin resistance. Elevated levels of leptin and insulin in the serum are linked to obesity, and therefore it is likely that they are responsible for the complex presentation of PCOD in obese patients.

Management

Since its etiology is not clear, PCOD prevention, is limited and management of the disease is primarily directed towards alleviating symptoms and manifestations. Management in perimenopausal women depends on their degree of hirsutism, obesity and other disorders. Therapeutic interventions, such as insulin sensitizers, oral contraceptive pills (OCP), should be directed towards addressing the individual needs and prevention of long-term complications. Long-term follow-up is needed to determine the effectiveness of these approaches in changing metabolic outcomes without causing unnecessary harm. OCP have several benefits in the treatment of irregular menstrual cycles and reduce hair growth in

nearly two – thirds of patients by decreasing ovarian and adrenal steroid production in hirsute women [49-52]. Lifestyle interventions are critical to the management of this disease. For example, cigarette smoking should be strongly discouraged as it exacerbates the already increased risk of atherosclerosis. In order to maintain a healthy weight, should maintain a healthy diet and regular exercise on a day-to-day basis. Weight loss during menopause is problematic without estrogen from the ovaries, the body has to rely on fat and the adrenal glands for hormone production. Furthermore, if there is additional insulin resistance, weight loss is difficult. However, even moderate weight loss in obese subjects can result in improved insulin sensitivity, reduction of hyperandrogenism, hirsutism, and improved menstrual function. In fact, weight loss should be the first line of management in obese patients. In order to keep symptoms controlled and to help promote a healthy life, a woman who is both menopausal and has PCOD needs to follow a strict exercise regimen and follow a diet that is lower in carbohydrates. Low carbohydrate diets may keep the weight off after menopause. Excess androgen production may have a profound influence on LH pulse frequency in women with PCOS. Administration of progesterone or OCP results in a greater suppression of mean LH and LH pulse frequency in normal women compared with women with PCOD [53, 54]. Eagleson [55] showed using an androgen-blocking agent prior to the administration of estrogen and progesterone to PCOD women resulted in the restoration of LH pulse frequency to that observed in normal women. Shayya [11] reported that in PCOD, LH secretion is relatively insensitive to progesterone inhibition because of high levels of circulating androgens. A reduction of hyperinsulinemia has been associated with significant decrease of serum androgens, without a corresponding change in LH, in women with PCOD treated with insulin-lowering drugs, and this indirectly suggests a role for insulin in LH-stimulated androgen synthesis. Shayya [11] also suggest that prevention of diabetes, MBS, and endometrial carcinoma is essential by treating detected abnormalities in various systems.

Douglas *et al.* [56] have shown that a moderate reduction in dietary carbohydrates reduced the fasting and post-challenge insulin concentrations, which over time may improve endocrine outcomes. OCPs showed

significantly better response in the form of regularization of menstruation and decrease in hirsutism compared to only metformin. Papunen *et al.* [57] demonstrated that regular menstruation and a measurable decline of hirsutism occurred in women who took OCPs than those who used only metformin. Legrgro [58] report that depot and cyclical oral medroxyprogesterone (10 mg) suppress pituitary gonadotropins and circulating androgens in women with PCOS. Insulin-sensitizing agents ameliorate insulin resistance and abnormalities in the endocrine, metabolic and reproductive systems, and metformin, a biguanide, has been extensively used. The actions of metformin are not associated with an increase in insulin secretion, and hypoglycaemia is not a risk. The weight loss that often accompanies protracted therapy may account for some of the beneficial effects. Fedorcsak [45] report women with PCOD treated with the insulin sensitizers Diazoxide and metformin had reduced Leptin levels, suggesting that improved insulin sensitivity and decreased circulating insulin levels diminish the insulin-mediated stimulation of leptin production among affected women. Kowalska *et al.* [59] also report that 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 as additional therapeutic options in obese women with PCOD. The reduction in 17 α -hydroxyprogesterone in response to challenges with gonadotropin releasing hormone (GnRH), human chorionic gonadotropin (hCG), and ACTH following short-term metformin therapy in obese and lean women with PCOD suggests that the reduction in ovarian and adrenal cytochrome p45017 α – enzyme activity may be responsible for the amelioration of hyperandrogenaemia in these women [60]. However, this finding has not been corroborated by other investigators [61, 62]. Pawelczyk *et al.* [63] report that metformin therapy not only restores normal levels of insulin and testosterone, but also decreases the pool of free, bioactive IGF-I by increasing the levels of circulating IGFBP-1. However, Wulffele *et al.* [64] report that metformin decreases plasma triglycerides, total cholesterol and LDL cholesterol more than control treatments but has no effect on other outcomes. Yen [47] report that the effect of metformin on modulating lipoprotein profile has not been convincing; while one long-term study has

demonstrated a moderate improvement in plasma triglyceride and LDL cholesterol concentrations, short-term administration has limited effects on women who have aberrant lipoprotein profiles at the outset.

Antiandrogens such as spironolactone, CPA, or flutamide are used and act by competitive inhibition of androgen-binding receptors or by decreasing androgen production [65].

Gonadotropins have the risk of hyperstimulation and require long courses of therapy at a considerable cost. The three LHRH agonists are: D-Ser (tBU) Gly LHRH ethylamide, which come in the form of a nasal spray, D-Trp6-LHRH, administered by daily intramuscular injections; and the long-acting preparation, D Trp6 LHRH, is given monthly intramuscular injection. They have similar efficacy in their ability to downregulate the pituitary-ovarian axis [66]. 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.* [66] reported that the immunoreactive LH-reducing effect of the LH-RH agonists was true only if the basic levels of the hormone were higher than 11mIU/ml. Isolated ovarian surgery is considered in refractory cases but may be ovarian surgery is as effective as no therapy in perimenopausal women!

Long-term management

The management should include patient education and special attention should be paid the risk for to diabetes, cardiovascular problems, obesity and endometrial cancer.

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