Exercise and Polycystic Ovary Syndrome.

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Exercise in women with Polycystic Ovary Syndrome (PCOS)

This chapter will summarise the current research on using exercise to manage PCOS.

Chapter 5. Exercise as treatment in women with Polycystic Ovary Syndrome (PCOS)

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Abstract

Polycystic Ovary Syndrome (PCOS) is a complex endocrinopathy, affecting both the metabolism and reproductive system of women of reproductive age. Prevalence ranges from 6.1% to 19.9% depending on the criteria used to give a diagnosis. PCOS accounts for approximately 80% of women with anovulatory infertility. PCOS causes disruption at various stages of the reproductive axis. Evidence suggests lifestyle modification should be the first line of therapy for women with PCOS. Several studies have examined the impact of exercise interventions on reproductive function, with results indicating improvements in menstrual and/or ovulation frequency following exercise. Enhanced insulin sensitivity underpins the mechanisms of how exercise restores reproductive function. Women with PCOS typically have a cluster of metabolic abnormalities that are risk factors for CVD. There is irrefutable evidence that exercise mitigates CVD risk factors in women with PCOS. The mechanism by which exercise improves many CVD risk factors is again associated with improved insulin sensitivity and decreased hyperinsulinemia. In addition to cardiometabolic and reproductive complications, PCOS has been associated with an increased prevalence of mental health disorders. Exercise improves psychological well-being in women with PCOS, dependent on certain physiological factors. An optimal dose-response relationship to exercise in PCOS may not be feasible because of the highly individualised characteristics of the disorder. Guidelines for PCOS suggest at least 150 minutes of physical activity per week. Evidence confirms that this should form the basis of any clinician or healthcare professional prescription.

Keywords

Polycystic ovary syndrome, exercise, physical activity, reproductive health, cardiovascular disease

1. Background

1.1 Diagnosis and Prevalence

Polycystic Ovary Syndrome (PCOS) is a complex endocrinopathy affecting both the metabolism and reproductive system in women of reproductive age [1] . Currently, three sets of diagnostic criteria exist; 1) the National Institutes of Health (NIH) criteria from 1990, 2) the American Society of Reproductive Medicine sponsored European Society of Human Reproduction and Embryology (ASRM/ESHRE) criteria revised in 2003, and 3) the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society criteria from 2009 [2]. Each of the criteria is predicated on the presentation of the main characteristics of PCOS; polycystic ovaries (PCO), clinical or biochemical hyperandrogenism (excessive levels of androgens), and chronic oligo-anovulation (infrequent or absent ovulation) [2].

The NIH criteria indicates that chronic anovulation and clinical or biochemical hyperandrogenism must both be present [3]. The ASRM/ESHRE criteria is known as the Rotterdam criteria, named after the place where the consensus meeting was held. The criteria states that of the main characteristics (PCO, clinical or biochemical hyperandrogenism, and chronic oligo-anovulation), any two of the three could be present [4]. Both of the aforementioned criteria stipulate that other disorders that could be responsible for these symptoms must be excluded first, such as congenital adrenal hyperplasia, Cushing's syndrome, which is a condition caused by excessive adrenal production of cortisol, androgen secreting tumours and hyperprolactinemia, where an individual has excessive serum levels of prolactin [2]. The more recent AE-PCOS criteria is based on three conditions: hyperandrogenism (clinical or biochemical), ovarian dysfunction (encompassing both PCO and oligo-anovulation) and the exclusion of other androgen excess related disorders [5].

The prevalence of PCOS therefore depends on which criteria is used. Reports of prevalence range from 6.1% to 19.9% [6]. Table 1 indicates reported prevalence from studies using different diagnostic criteria in Australia [7], Turkey [6] and Iran [8].

Table 1. Prevalence of PCOS (%) based on individual criteria*

	Diagnostic Criteria		
	NIH[a]	AES[b]	Rotterdam[c]
March et al. [7]	8.7	12.0	17.8
Yildiz et al. [6]	6.1	15.3	19.9
Mehrabian et al. [8]	7.0	7.9	15.2

* adapted from Burks & Wild [2]

[a]National Institutes of Health international conference 1990

[b] Androgen Excess Society diagnostic criteria 2009

[c]Task force sponsored by the European Society of Human Reproductive and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), 2003

It is clear from the data in table 1 that the Rotterdam criteria is the least restrictive, because the NIH and AE-PCOS criteria both consider hyperandrogenism as a central facet in the pathogenesis of PCOS indicating this should be present along with PCO or oligo-anvoluation [9]. The Rotterdam criteria allows for additional phenotypes of PCOS, such as those with PCO and menstrual irregularity without hyperandrogenism. Nevertheless, it can be considered as an emerging epidemic that needs to be attenuated due to numerous debilitating symptoms and co-morbidities.

1.2 Associated Symptoms and Co-morbidities

Though not acknowledged in the diagnostic criteria, women with PCOS often have higher amounts of visceral fat (around the organs in the peritoneal cavity) [10], up to 80% prevalence of insulin resistance [11] and up to 70% prevalence of dyslipidemia [12]. PCOS is associated with reproductive and cardiometabolic complications and increased risk of cardiovascular diseases (CVD); forty percent of women with PCOS are affected by infertility [13], while there is a two to four-fold higher incidence of metabolic syndrome in the PCOS population in comparison to weight-matched healthy women [14]. This is primarily true for those phenotypes presenting with hyperandrogenism; this phenotype has been associated with a metabolic profile that encompasses higher incidences of insulin

resistance and a worse lipid profile than those women with a normo-androgenic profile, despite comparable distributions of body weight [15].

It is hypothesised that insulin resistance underpins this worse metabolic profile rather than androgen excess itself. Insulin acts as a co-gonadotropin, stimulating the ovary to produce testosterone, whilst simultaneously inhibiting the production of sex hormone binding globulin (SHBG) which leads to a higher concentration of bio-available testosterone [16]. Additionally hyperinsulinemia can lead to hepatic overproduction of very low density lipoproteins (VLDL), and elevation in triglycerides (TG) through decreased lipoprotein lipase-mediated lipolysis, leading to increased circulating chylomicrons and VLDL [17]. Skeletal muscle insulin resistance may also promote dyslipidemia by re-directing dietary carbohydrate sources away from skeletal muscle glycogen synthesis into hepatic de novo lipogenesis, and subsequently increased circulating triglycerides assembled from glucose substrates and a reduction in high-density lipoprotein (HDL) concentrations [18].

1.3 Treatment

It is difficult to isolate a single disruptive factor for treatment, since PCOS is often presumed to be the result of an endocrine system feedback loop [19]. In addition, the individual presentation of PCOS symptoms, resulting in various phenotypes, play a role in the treatment chosen. Because of the complex pathophysiology of PCOS, treatment ranges from pharmacological to alternative therapies such as acupuncture [20]. Pharmacological options include biguanides to improve insulin sensitivity, the oral contraceptive pill to restore menstrual regularity, clomiphene to induce ovulation, and statins to lower blood cholesterol [21].

Lifestyle modification should be the first line of therapy for women with PCOS [22]. Interventions that target insulin sensitivity and, for women with obesity and PCOS, promote weight loss are a critical in the management of the condition [23]. Recent research indicates that exercise of a moderate intensity (~50-70% VO_{2max}), for approximately 12 weeks, produces improvement in cardiometabolic risk factors, including blood pressure, TG, insulin resistance and inflammation, and reproductive outcomes such as increased ovulation rates and greater responsiveness to IVF [10,24].

The remainder of this chapter will outline and describe current research examining the effects of exercise on cardiometabolic, reproductive and mental health outcomes in women with PCOS.

2. Exercise and PCOS

2.1. Reproductive Function

PCOS accounts for approximately 80% of women with anovulatory infertility [25]. PCOS causes disruption at various stages of the reproductive axis, including the hypothalamus-pituitary axis, leading to inappropriate regulation of ovarian steroidogenesis and folliculogenesis [26]. The key neuroendocrine abnormalities involved in PCOS are increased gonadotropin-releasing hormone (GnRH) pulsatile activity, leading to disproportionate levels of luteinizing hormone (LH) in comparison to follicle-stimulating hormone (FSH) [26], known as the LH:FSH ratio. In turn, overproduction of LH stimulates ovarian theca cell hyperactivity, culminating in increased ovarian steroidogenesis. The lack of FSH stimulation of granulosa cell development and aromatase production means that the androgens are not converted to oestrogen, and disruption of follicle maturation and ovulation occurs [27,28].

2.1.1 Effects of exercise on reproductive function in women with PCOS

Several studies have explored the impact of exercise interventions on reproductive function, with results indicating improvements in menstrual and/or ovulation frequency following exercise in comparison to diet or control groups [29,30,31]. These improvements included a change from non-ovulatory to ovulatory cycles, restoration of cycle regularity and improvement in inter-cycle variation [24] indicating that exercise may be more beneficial to reproductive function than caloric restriction alone. Evidence suggests that the pregnancy rate among women with PCOS undertaking an exercise intervention is 35% [31], with pregnancy being a common reason for drop-out amongst participants with PCOS in exercise trials [32]. It has been noted that lifestyle modification for overweight or obese infertile women with PCOS is a cost-effective solution for those women wishing to conceive, either as a primary intervention or in conjunction with fertility treatment [33].

It has been suggested that the type and frequency of exercise is not important in improving reproductive function in PCOS [24], but contradictory findings suggests otherwise. A recent feasibility trial examining the effects of progressive resistance training (PRT) on women with PCOS found PRT to be effective at improving cardiometabolic outcomes, but found no such effect on reproductive outcomes [34]. The optimal type or intensity of exercise needed in order to elicit a response from the reproductive system remains to be elucidated. However, there is an insufficient number of studies that examine the impact of resistance training in PCOS [32].

Weight loss does not appear necessary to achieve improvements in reproductive function. However, a weight loss of as little as 5% may improve spontaneous ovulation rates, reduce associated metabolic complications and increase chances of conception [35]. In addition, optimisation of body mass index (BMI) into the 'healthy' range for women with obesity or overweight may attenuate the risk of pregnancy-related complications in women with PCOS, including gestational diabetes, hypertensive disorders and premature delivery [36].

Therefore, for the two-thirds of women with PCOS with overweight or obesity, an exercise intervention intended to maximise weight loss may offer additional benefits. This can also be important for those overweight women with PCOS, intending to undertake fertility treatment. Excess body mass can blunt the response to treatment and higher doses of ovulation-inducing medications may be needed [25]. Subsequently, exercise with concurrent weight loss may be optimal and cost-effective in these cases. If weight loss is to be targeted through exercise interventions, greater weight loss is achievable with an intervention of a duration of at least six months [24].

2.1.2 Mechanism of Action

In keeping with the presumption of PCOS occurring as a result of an endocrine feedback loop, it is not immediately clear whether neuroendocrine abnormalities are a cause or consequence of PCOS [26]. In normal menstrual physiology, both estradiol (depending on the stage of folliculogenesis) and testosterone provide negative feedback to the hypothalamus to inhibit the frequency and amplitude of the GnRH pulse [37]. In PCOS, it appears that persistent elevated androgen levels may decrease the

sensitivity of the GnRH pulse activator to inhibition by ovarian steroids, preventing the normal negative feedback suppression of LH [37,38].

The hyperandrogenemic milieu, exacerbated by hyperinsulinemia, may over-stimulate the growth and recruitment of antral follicles, which in turn may lead to threefold higher concentrations of anti-Mullerian hormone (AMH), produced by granulosa cells, in women with PCOS compared to healthy women [39]. AMH reduces follicular sensitivity to FSH and serves a purpose to prevent the depletion of all primordial follicles at once [40]. However, elevated concentrations may disrupt folliculogenesis by inhibiting aromatase and preventing the selection of a dominant follicle, resulting in follicular arrest at the small antral stage [39].

Enhanced insulin sensitivity underpins the mechanisms of how exercise restores reproductive function [24]. Reducing hyperinsulinemia decreases ovarian steroidogenesis and increases SHBG, and the resulting return to a normo-androgenic environment may restore sensitivity of the GnRH pulse activator to steroid inhibition of LH. Subsequently, decreased levels of LH and androgens may halt the excessive recruitment of antral follicles, allowing a dominant follicle to mature, eventually leading to ovulation.

Weight loss in PCOS, either with or without exercise, can lead to reductions in visceral fat as indicated by improvements to waist-to-hip (WHR) ratio, a measure which is strongly correlated with insulin resistance [24]. Indeed, studies reporting a reduction in WHR have also reported reductions of fasting insulin [24]. Subsequently, the resultant reduction in circulating androgens may explain the additional benefits of weight loss in overweight or obese women with PCOS.

3.1 Cardiometabolic Outcomes

Women with PCOS typically have a cluster of metabolic abnormalities that are risk factors for CVD. These include obesity, metabolic syndrome, impaired glucose tolerance, hypertension, impaired endothelial and myocardial function, and dyslipidemia [14,41,42]. Evidence suggests that sub-clinical atherosclerosis, indicated by carotid intima-media thickness (cIMT), is higher in women with PCOS compared to weight-matched controls [41,43]. Additionally, PCOS is associated with increased low-

grade inflammation, with higher circulating concentrations of many inflammation markers that mediate CVD, such as C-reactive protein, increased white cell count, neutrophil/lymphocyte ratio, tumour-necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6) [44,45,46,47,48,49]. It follows that women with PCOS have a 50% increased risk of CVD events compared to weight-matched counterparts [14] and that the rate of diabetes is 2.6 times higher than that of the general female population [50].

There has been a lot of discussion on whether the increased association with CVD risk factors is due to PCOS itself, or whether it is due to the associated obesity. Indeed, the increased rate of diabetes in women with PCOS positively correlated with BMI [50]. However, while obesity may certainly be an exacerbating factor [19], it is estimated that at least half of women with PCOS are not overweight or obese [50]. As evidenced by those risk factors that are increased in comparison to weight-matched healthy women, there are clearly additional mechanisms underlying the increased CVD risk in PCOS. Nevertheless, a common feature in both overweight and lean women with PCOS is central adiposity [16]; the tendency for fat to accumulate around the abdominal area, including both visceral fat and the subcutaneous fat present underneath the skin. A woman with a BMI within the 'healthy' range could still exhibit abdominal obesity due to excessive visceral fat. This type of body composition may contribute to insulin resistance because visceral fat secretes IL-6, an adipokine that inhibits insulin-mediated glycogenesis and stimulates hepatic (liver) gluconeogenesis [51].

3.1.1 Effects of Exercise on Cardiovascular Disease Risk Factors in women with PCOS

There is irrefutable evidence that exercise mitigates CVD risk factors in healthy populations [52], populations with dyslipidemia [53], populations with metabolic syndrome [54,55], and in women with PCOS [56]. One of the most prominent studies is the case-control INTERHEART study, which found moderate to vigorous intensity exercise to be one of nine lifestyle modifications that are protective against myocardial infarction (heart attack) [57]. However, some studies have produced inconsistent results with respect to the effectiveness of exercise only, without any additional dietary or pharmacological interventions, in improving biomarkers of CVD risk: This is particularly true regarding cholesterol and lipoprotein concentrations [10], and inflammation [58].

Longer exercise interventions (e.g. >20 weeks; [54,55,59]) are associated with improved lipid profile, and the reversal of metabolic syndrome in healthy populations. This might account for some of the discrepancy in PCOS research, with exercise interventions typically ranging from eight to 24 weeks in duration. PCOS studies with longer intervention durations have found improvements in VLDL and HDL [60], whereas shorter interventions have found no change in LDL and HDL, despite improvements in cardiorespiratory fitness [10]. In order to promote changes to blood lipids in a shorter duration, the addition of a dietary component may make this achievable [30].

Exercise interventions for 12 weeks, 3 sessions per week, can promote weight loss and reductions in BMI in women with PCOS [10]. These changes are typically associated with a reduction in WHR or waist circumference, indicating a decrease in abdominal obesity. Waist circumference and WHR may be a better indicator of health than BMI alone because of its association with other CVD risk factors, such as impaired glucose metabolism [57,61]. While changes to BMI and waist circumference seem to be more effectively reduced with combined exercise and dietary interventions in comparison to dietary intervention alone, weight loss is still achievable in shorter exercise-only interventions [24]. However, the amount of weight lost seems to be proportionately related to duration of the intervention [10] Longer duration (20 weeks+) may be the key to promote greater weight loss, irrespective of type and frequency of exercise [30].

In the INTERHEART study, hypertension is well recognised as a CVD risk factor, stated as one of the main modifiable risk factors responsible for most incidents of myocardial infarction [57]. Hypertension is one of the key characteristics of metabolic syndrome, and there is an inverse relationship between blood pressure and insulin sensitivity [54]. Evidence supports the role of exercise as treatment for hypertension, with exercise training decreasing blood pressure in around 75% of hypertensive adults, with a more pronounced affect in women [62].

In women with PCOS, the results are less clear; some studies find no statistically-significant improvements in systolic blood pressure (SBP) or diastolic blood pressure (DBP) in exercise interventions from 12 to 24 weeks [63,64], while others have found small, but clinically-meaningful, improvements in SBP with exercise or exercise in combination with dietary intervention [30,65].

These conflicting results may be due to the wide range of phenotypes possible under the PCOS diagnostic criteria; indeed, prevalence of hypertension in PCOS is reported to be between 5.5-12% [66,67] and as such many PCOS participants may be normo-tensive.

Finally, there is much evidence to support the role of exercise as treatment for one of the most common metabolic aberrations of PCOS: insulin resistance. PCOS research supports the role of exercise in improving insulin sensitivity immediately after an acute bout of exercise [68], but also in the long-term with exercise interventions from three months [65,69] to 20+ weeks [30,31]. Insulin resistance has been linked to abdominal obesity, hypertension, the development of type II diabetes (T2D) [70], dyslipidemia, and inflammation [71], meaning it is a key indicator of CVD risk in women with PCOS, where the prevalence of insulin resistance is up to 80% [11], independent of weight. Improvements in insulin sensitivity and/or hyperinsulinemia in PCOS have been associated with lowered androgen concentrations [72] and improvements in many of the other CVD risk factors mentioned previously [24,73], providing support for the role of insulin resistance as a key, underpinning mechanism in the pathophysiology of PCOS.

3.1.2 Mechanisms of Action

The mechanism by which exercise improves many CVD risk factors is again associated with improved insulin sensitivity and decreased hyperinsulinemia. In PCOS, the cause of insulin resistance is hypothesised to be caused by a post-receptor defect in insulin signalling, where phosphorylation of insulin-receptor substrate -1 (IRS-1) serine residues is increased while the phosphorylation of the tyrosine residues is decreased [72]. This exaggerated serine phosphorylation may cause a decrease in insulin-stimulated IRS-1 activation and subsequently a decrease in translocation of glucose transporter 4 (GLUT4), the insulin sensitive glucose transport protein, leading to decreased cellular glucose uptake [74,75].

The pro-inflammatory cytokine TNF-a is elevated in PCOS independent of obesity, and TNF-a is a known mediator of insulin resistance by inducing the exaggerated serine phosphorylation of IRS-1 [75]. TNF-a is produced by visceral adipose tissue [76], and this increased distribution of intra-

abdominal fat has been shown to be more prevalent in women with PCOS compared to weight-matched controls [77]. In addition, intra-abdominal fat releases more free-fatty acids (FFA) into circulation than subcutaneous fat [74], and the increased availability of FFA may lead to storage of lipids in non-adipose tissue such as muscle cells, leading to lipotoxicity and inflammation [71,72,78]. The accumulation of these intra-myocellular lipid metabolites (such as diacylglycerols and ceramides) have been postulated to activate intra-cellular serine kinases which may be key to the insulin-signalling pathway defect that results in insulin resistance [72,78] Women with PCOS have been shown to have increased FFA availability [78].

Obesity in PCOS also exacerbates insulin resistance and inflammation due to hypoxia-related adipocyte death, resulting from adipose tissue expansion. This leads to mononuclear-cell (MNC) infiltration which become macrophages, subsequently releasing TNF-a and IL-6, contributing to insulin resistance [71,75]. However, even in the absence of obesity, MNC sensitivity to glucose is increased in PCOS, and glucose ingestion promotes an inflammatory response [75].

Exercise improves glucose and insulin metabolisms by restoring glucose homeostasis through increased skeletal muscle glucose disposal [79]. This is achieved via increases in: i) skeletal muscle capillarisation, ii) expression of glucose transporter proteins, and iii) mitochondrial function [80]. Indeed, exercise-mediated glucose disposal does not rely on insulin receptor or IRS-1 phosphorylation as in normal insulin signalling, but does so through distinct proximal signalling mechanisms [79]. Chronic exercise increases mitochondrial content and activity, and this is associated with improved skeletal muscle insulin sensitivity and whole body metabolic health [80]. A possible mechanism for this is the increased mitochondrial lipid oxidation of intra-myocellular lipid metabolites, which interfere with insulin signalling [78]. The subsequent improvement in insulin sensitivity may therefore reduce inflammation and the release of cytokines that promote insulin resistance. In addition, as previously outlined, weight loss (in particular a reduction in abdominal obesity) is often associated with exercise in PCOS [24], and this reduction of the metabolically active visceral adipocytes may also lead to reduced secretions of TNF-a and IL-6.

The resulting improvement in insulin metabolism may lead to improved lipid profile through decreased mobilisation of FFA through lipolysis, and the increased uptake and storage of glucose and triglycerides [71]. Blood pressure may also be reduced by improving insulin sensitivity. In the insulin-resistant state, compensatory hyperinsulinemia results in vasoconstriction and increased sodium reabsorption which lead to hypertension [54,71]. Thus, exercise bestows a multitude of positive effects that reduce many of the CVD risk factors associated with PCOS.

4.1 Mental Health and Psychological Wellbeing

In addition to a multitude of cardiometabolic and reproductive complications, PCOS has been associated with an increased prevalence of mental health disorders [81,82,83,84,85,86] . PCOS symptomology includes a number of features that are associated with poor body image and decreased quality of life, such as obesity, acne, excess body hair growth, scalp hair thinning, infertility and menstrual irregularity [82].

Research has long identified a link between women with PCOS and increased incidences of depression and anxiety [81]; a recent report suggests that the odds ratio (OR) for women with PCOS compared to controls for depression and anxiety is 1.26 and 2.76, respectively [82]. In China, a study of 120 patients with PCOS and 100 controls reported the prevalence of anxiety and depression to be 13.3% and 27.5% in PCOS compared to 2% and 3% in controls [83]. Similarly, a study in India of 110 PCOS patients and 40 controls identified the prevalence of major depressive disorder and generalised anxiety disorder (GAD) to be 23.64% and 15.45% in PCOS, compared to 7.5% and 0% in controls [85]. The increased prevalence of mental health disorders is not limited to depression and anxiety. Reports also indicate an increased prevalence of bipolar disorder [87], personality disorders [86] and binge eating disorders [88].

4.1.1 Effects of Exercise on Mental Health in women with PCOS

The benefits of exercise on psychological well-being, including improvements in mood, reduced

depressive symptoms, and improved body-image and quality of life are documented in overweight women [89,90] and adults in general [91,92]. However, this is less well-documented in women with PCOS. While various studies have assessed the impact of an exercise intervention on health-related quality of life (HRQoL) in PCOS, these have mostly been combined 'lifestyle' interventions with exercise undertaken as an adjunct to different diets [93,94] or drug therapy [95].

Other studies have compared exercise alone with other treatment groups, rather than a standard-care or control group [96]. These include the comparison of exercise with both an acupuncture group and a control group [97], and the comparison of a traditional exercise programme with yoga among adolescents [98]. Despite not being able to isolate the effects of exercise independently, most interventions including exercise improved HRQoL, anxiety or self-esteem [93,94,97,98], suggesting that exercise has a place in a lifestyle intervention aimed at improving mental wellbeing in women with PCOS [96].

Moreover, cross-sectional and observational studies lend support to the idea that physically active women with PCOS are likely to have less severe depression, or no depression, compared to inactive women with PCOS [99,100]. The psychological benefits of exercise are not necessarily related to weight loss since an observational study of women with PCOS found that those completing a self-directed brisk walking programme improved their body image significantly in comparison to those women who did not complete the walking intervention, despite no changes to BMI [101].

4.1.2 Mechanisms of Action

The mechanisms by which exercise improves psychological well-being in women with PCOS is dependent on certain physiological factors. For example, various studies suggest increased mental distress related to body image in women with overweight or obesity [84,101]. Exercise interventions (combined with diet) that result in weight-loss lead to improved self-esteem and HRQoL [93,94]. As outlined previously in the chapter, exercise and associated weight-loss may also improve fertility which is another factor that improves HRQoL. Improvements in BMI may also reduce sleep disturbances which affect day-to-day functioning [84]. For example, obstructive sleep apnea (OSA) is

closely related to obesity and insulin resistance, and weight loss is a key treatment of this condition, which may increase sleep duration [102]. Indeed, research reports that women with PCOS may be 30 times more likely to experience sleep disordered breathing than controls [103].

Another physiological factor may be the cycle of inflammation and impaired insulin metabolism present in PCOS that has been described previously. Clinical and experimental evidence links activation of the brain cytokine system to depression [104] and may be a factor in the increased prevalence of depression in PCOS. Subsequently, interventions that reduce obesity-related inflammation or normalise insulin metabolism to the effect of reducing pro-inflammatory cytokines, may reduce rates of depression. In addition, severity of hyperandrogenism experienced by the individual may be related to higher levels of mental stress in PCOS because of the clinical presentation. That is, cystic acne, hirsutism and thinning scalp hair which may lead to negative self-image and poor self-esteem [81,84]. Exercise can restore insulin sensitivity and thus reduce hyperinsulinemia [24], which causes ovarian steroidogenesis and reduces hepatic output of SHBG, leading to hyperandrogenemia. The subsequent reduction in androgens may therefore improve the related clinical symptoms and improve body-image.

Finally, research indicates that women with PCOS may have enhanced hypothalamus-pituitary-adrenal (HPA) axis activity in response to stress, characterised by markedly increased psychological distress, which may provide a link between PCOS and the increased prevalence of mental health disorders [105]. Habitual physical activity may modulate the sympathetic nervous system's response to stress and therefore reduce the negative impact of stress on health [106,107].

5. Translating Evidence into Practice: Exercise Programming

The summary of current research outlined in this chapter provides compelling evidence that exercise can be used to alleviate or mitigate many of the cardiovascular, metabolic, reproductive and psychological aberrations that are associated with PCOS. While a single, unifying theory of the cause of this disorder is yet to be found, the main theories for the aetiology of PCOS include primary disordered gonadotropin secretion, primary ovarian and adrenal hyperandrogenism, and primary

insulin resistance [28]. Whichever the true cause may be, exercise has been shown to play a role in normalising symptoms associated with each suggested aetiology.

An optimal dose-response relationship to exercise in PCOS may not be feasible because of the highly individualised characteristics of the disorder. Indeed, the AE-PCOS Society suggests that individualised exercise programmes may improve compliance, and suggest group or home exercise [108].

Specifically, Australian guidelines for PCOS suggest at least 150 minutes of physical activity per week [109]. This is in line with current UK physical activity guidelines for adults aged 19-64 years, and this should form the basis of any clinician or healthcare professional prescription. Most research examining the effects of exercise on PCOS symptoms is aerobic such as walking, jogging, running and / or cycling [24,56,110]. For example, many of the benefits associated with exercise can be obtained by brisk walking, defined as faster than normal walking but at a pace that could be sustained for at least 20 minutes, and this is also the mode suggested by the AE-PCOS Society [101,108].

Metabolic improvements are possible in as little as 12-weeks [10]. However, if weight-loss and/or improvement to lipid profile is also recommended, women with PCOS should undertake exercise programmes of longer duration (20+ weeks), and/or consider the inclusion of a dietary component to achieve the best results, regardless of type or frequency of the exercise [30,54,55,64].

Higher-intensity exercise (90-100% VO_{2max}) is less well-documented. However, positive improvements to insulin metabolism have been shown with high-intensity interval training sessions in PCOS [10,111]. In addition, PRT is a mode of exercise that complementary to its effectiveness in treating insulin resistance, may also decrease the loss of fat-free mass (FFM) and increase lean body mass, whilst simultaneously reducing waist circumference [34,112]. This may be a particularly important consideration for older women at risk of sarcopenia [113].

Regardless, an effective exercise programme that is engaging and that women with PCOS will adhere to is one that is client-centred, offering a choice of modes that may suit a variety of women of different physical abilities and preferences. In addition, the presence and support of other people may

be a contributing factor to the compliance of an exercise programme, and group or supervised exercise sessions should be considered in addition to solitary exercise [96].

6. Practical Considerations for Exercise Prescription in PCOS

It is important to consider the practical applications of exercise prescription for women with PCOS. Below are some key points to keep in mind to maximise adherence to an exercise intervention:

1. Consider that the client may have issues or anxieties surrounding body-image and self-esteem. As such, individual exercise sessions or small groups within private facilities may be more effective than large, publicly accessible gym spaces.
2. Clients should be informed of the benefits of exercise and physical activity even in the absence of weight loss, such as improved cardiovascular and metabolic health and increases in mental health and wellbeing.
3. Enjoyment should be a key tenet of an exercise intervention; try to ask the client about previous exercise modes they have enjoyed and implement these.
4. Undertake individual fitness testing and assessment before commencement of the programme and use the results to set bespoke training thresholds for the client. This will avoid discomfort from over-exertion which may increase injury risk and impact adherence.
5. In addition, if the client is not or has not been a habitual exerciser, begin training at low aerobic thresholds, i.e. 55-60%HR_{max} and increase the thresholds as the individual adapts to the demands of exercise.
6. For very untrained individuals, intermittent activity with regular breaks may be more achievable at first.
7. If increased risk for CVD is present, such as hypertension and T2D, close monitoring of heart rate and rate of perceived exertion (RPE) is recommended.

7. Key Points

- PCOS is a complex endocrinopathy affecting up to 20% of reproductive-aged women. It is associated with cardiometabolic and reproductive complications. Symptoms may be exacerbated by obesity.
- Insulin resistance is a key underpinning feature and exercise programmes that attenuate insulin resistance or hyperinsulinemia may be integral to improving associated symptoms.
- Research shows that exercise can improve reproductive function, cardiovascular and metabolic health, and mental well-being.

  Weight loss is not necessary for health improvements, and clinicians and healthcare professional should use the minimum physical activity guidelines as a basis to prescribe exercise.

  - Future research may be beneficial in indicating the efficacy of different exercise intensities, such as high-intensity exercise and progressive resistance training.

Competing financial interests

The authors declare no competing financial interests.

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