

## REVIEW

## Obesity and polycystic ovary syndrome

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## Abstract

The increased global prevalence of obesity over the last 40-years has driven a rise in prevalence of obesity-related co-morbidities, including polycystic ovary syndrome (PCOS). On a background of genetic susceptibility, PCOS often becomes clinically manifest following weight gain, commonly during adolescence. A common endocrinopathy affecting between 6%-10% of reproductive-age women, PCOS presents with the cardinal features of hyperandrogenism, reproductive and metabolic dysfunction. PCOS associates with insulin resistance, independently of (but amplified by) obesity. Insulin resistance in PCOS is characterized by abnormal post-receptor signalling within the phosphatidylinositol-kinase (PI3-K) pathway. Multiple factors (including most notably, weight gain) contribute towards the severity of insulin resistance in PCOS. Compensatory hyperinsulinaemia ensues, resulting in over-stimulation of the (intact) post-receptor mitogen-activated protein kinase (MAP-K) insulin pathway, with consequent implications for steroidogenesis and ovarian function. In this concise review, we explore the effects of weight gain and obesity on the pathogenesis of PCOS from the perspective of its three cardinal features of hyperandrogenism, reproductive and metabolic dysfunction, with a focus on the central mediating role of the insulin pathway. We also consider key lifestyle strategies for the effective management of obese and overweight women with PCOS.

## KEYWORDS

metabolism, obesity, polycystic ovary syndrome

## 1 | INTRODUCTION

Over the last 40 years, the global prevalence of obesity in women has increased 2.5-fold from 6% to 15%.<sup>1</sup> Over a similar timeframe, the prevalence of obesity-related co-morbidities, of which there are >50 that collectively account for a substantial global health and socio-economic burden,<sup>2-4</sup> has increased commensurately. The development of many obesity-related conditions is mediated through the deleterious effects of insulin resistance (a consequence of weight gain) or compensatory hyperinsulinaemia, and its associated

metabolic dysfunction.<sup>5</sup> These include features of the metabolic syndrome (type 2 diabetes mellitus [T2D], dyslipidaemia and hypertension) and obesity-related malignancies such as endometrial carcinoma.<sup>6</sup>

Polycystic ovary syndrome (PCOS) is an important and highly prevalent obesity-related comorbidity,<sup>7</sup> that develops in girls and women who are genetically predisposed to its development.<sup>8-11</sup> PCOS affects between 6%-10% of reproductive-age women<sup>12-15</sup> and often develops during adolescence.<sup>3</sup> PCOS manifests with the typical clinical features of hyperandrogenism (including acne, hirsutism

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and male-pattern alopecia) and reproductive dysfunction (including oligo-amenorrhoea and associated sub-fertility).<sup>16</sup> Although not a constituent of its diagnostic criteria,<sup>17</sup> metabolic dysfunction also often forms an important component of the clinical presentation of PCOS. There are also characteristic biochemical and radiological features.<sup>18</sup>

The close association between obesity and PCOS is supported by epidemiological data, revealing that between 38%-88% of women with PCOS are either overweight or obese.<sup>3,19,20</sup> A meta-analysis of relevant studies reported in the literature showed that women with obesity had an odds ratio of 2.77 for the development of PCOS compared with their non-obese counterparts.<sup>21</sup> Furthermore, data from the Northern Finland Birth Cohort (NFBC) 1966 reveal associations between Body Mass Index (BMI) and features of PCOS at all ages,<sup>22</sup> and between an early rebound of adiposity in childhood and the subsequent development of PCOS (and obesity) in adulthood.<sup>23</sup> Such epidemiological data that support an association between obesity and PCOS are further corroborated by evidence from genetics studies that suggest an important role for gene variants implicated in the determination of fat mass (such as variants within the *FTO* gene<sup>24-29</sup>), as a mechanistic link for the development of PCOS. A genome-wide meta-analysis of PCOS also confirmed evidence for a shared genetic architecture between obesity, various metabolic traits and PCOS.<sup>30</sup> Such genetic effects on fat mass are likely to contribute towards the overall heritability of PCOS.<sup>5</sup>

Following an overview of insulin resistance in PCOS, we explore the complex pathogenesis of PCOS, including its mediation through the obesity-related insulin pathway,<sup>3</sup> from the perspective of each of its main features: metabolic dysfunction, hyperandrogenism and reproductive dysfunction. We also consider key lifestyle strategies for the effective management of obese and overweight women with PCOS.

## 1.1 | Insulin resistance in PCOS

Insulin resistance is present in many, if not most, women with PCOS.<sup>31-33</sup> Although the mechanism of insulin resistance in PCOS remains incompletely understood, the underlying defect is reported to occur within the post-receptor phosphatidylinositol 3-kinase (PI3-K) insulin pathway that mediates the metabolic effects of insulin.<sup>3</sup> Other factors may also contribute towards the establishment of insulin resistance in women with PCOS. These include increased levels of plasma testosterone (both in adulthood and prenatally, with evidence of the latter from an ovine model of PCOS<sup>34</sup>) and enhanced sensitivity of the androgen receptor (determined by the androgen receptor CAG repeat number).<sup>35</sup> Furthermore, suppressed levels of serum adiponectin in women with PCOS compared with BMI-matched control women (demonstrated in a large meta-analysis on >3400 subjects) may further contribute towards the establishment of insulin resistance in PCOS.<sup>36</sup> The role of high molecular weight adiponectin in PCOS remains incompletely understood<sup>37</sup> and should

form a focus for future research as there may be implications for therapy, as suggested by a recent study in a rodent model of PCOS.<sup>38</sup>

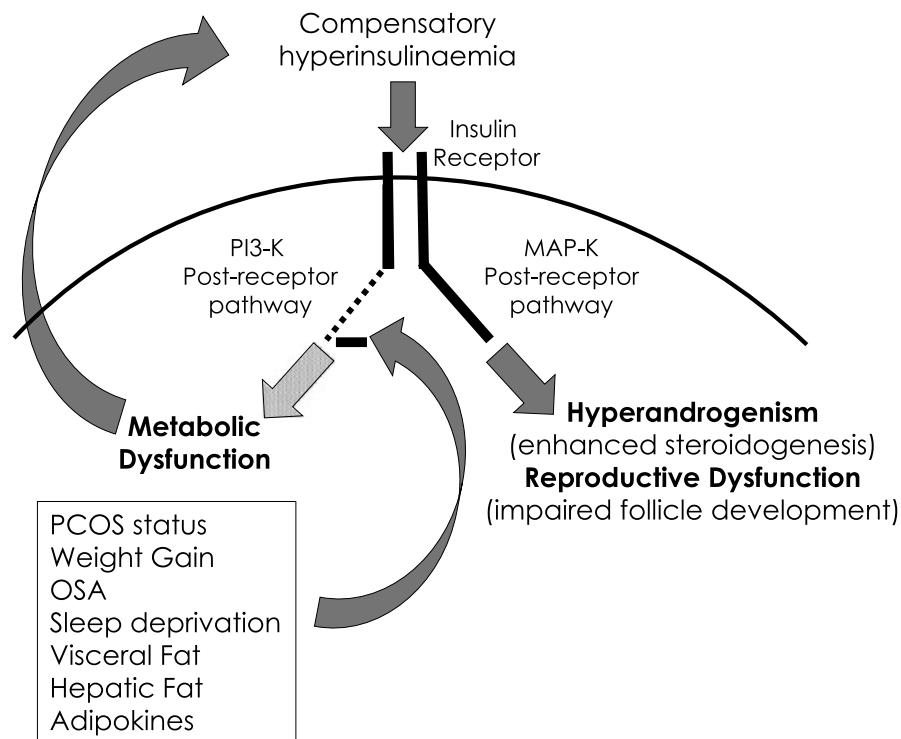
The severity of insulin resistance in women with PCOS is increased by subsequent weight gain,<sup>3,39</sup> possibly mediated through inflammatory pathways.<sup>40</sup> Similar to the insulin resistance that characterize T2D and PCOS, only the PI3-K post-receptor insulin pathway becomes resistant to the effects of insulin following weight gain and obesity.<sup>41</sup> Perhaps the umbrella term 'insulin resistance' should be replaced by the more descriptive term '*metabolic* insulin resistance',<sup>41</sup> that results from selective dysfunction of the PI3-K post-receptor insulin pathway in PCOS that is augmented commensurately with weight gain. Importantly, in both PCOS and obesity, the other main post-receptor insulin pathway, the 'mitogen-activated protein kinase' (MAP-K) pathway remains unaffected.<sup>3,42</sup> Compensatory hyperinsulinaemia ensues in an unsuccessful attempt to overcome the selective metabolic dysfunction stemming from the defective PI3-K insulin pathway.<sup>41</sup> The resulting preferential activation of the MAP-K post-receptor insulin pathway results in atherogenic, steroidogenic and mitogenic effects.<sup>43</sup> Furthermore, the preserved MAP-K insulin pathway confers much of the pleiotropic and deleterious effects of hyperinsulinaemia in obese women with PCOS that result in much of the hyperandrogenic and reproductive dysfunction that typify this condition (summarized in Figure 1).<sup>3,44</sup>

## 1.2 | The role of weight gain in the pathogenesis of metabolic dysfunction in PCOS

Although PCOS is associated with insulin resistance independently of obesity,<sup>3</sup> obesity greatly increases its prevalence and degree. Accordingly, PCOS also confers an increased risk for the development of T2D,<sup>7</sup> impaired glucose tolerance,<sup>45</sup> obstructive sleep apnoea (OSA),<sup>46</sup> dyslipidaemia and non-alcoholic fatty liver disease (NAFLD).<sup>47</sup> Such exposure to enhanced overall cardiometabolic risk likely translates into increased cardiovascular events and perhaps even premature mortality post-menopause. However, evidence to confirm such a hypothesis is currently deficient due to a lack of prospective and longer-term studies in women with PCOS that extend into post-menopause. This should form a focus for future research and would provide much insight into the temporal progression and metabolic legacy of PCOS beyond menopause, particularly regarding cardiometabolic risk and cardiovascular events and outcomes.

The hyperandrogenic and reproductive features of PCOS are driven primarily through the effects of compensatory hyperinsulinaemia on the ovary.<sup>48</sup> Conversely, the metabolic dysfunction and cardiometabolic risk that characterizes PCOS stems from a defective PI3-K post-receptor insulin pathway, the severity of which is influenced by body fat mass.<sup>3,49,50</sup> Given that the severity of compensatory hyperinsulinaemia associates with the defectiveness of the PI3-K post-receptor insulin pathway, this provides a hypothetical direct link between the severity of metabolic dysfunction and the hyperandrogenic and reproductive features of PCOS.

**FIGURE 1** Overview of the role of the post-receptor insulin pathways in the mediation of hyperandrogenism, reproductive and metabolic dysfunction in women with PCOS. MAP-K, Mitogen-Activated Protein Kinase; OSA, Obstructive Sleep Apnoea; PI3-K, Phosphatidylinositol 3-Kinase



The clinical and biochemical phenotype of PCOS is heterogeneous and that has a bearing on the manifestation of metabolic dysfunction. Studies on large and well-phenotyped cohorts have demonstrated confinement of insulin resistance (and associated features of the metabolic syndrome) to the subgroup of PCOS that manifest both hyperandrogenic and reproductive features.<sup>17,51</sup> Furthermore, the Rotterdam-defined diagnostic phenotypic subgroups with either hyperandrogenism or reproductive dysfunction alone had insulin sensitivity that was equivalent to that of women in BMI-matched control groups.<sup>17,51,52</sup> We also showed differences in BMI between the Rotterdam-defined phenotypic subgroups, those women with both hyperandrogenic and reproductive features having a significantly higher BMI than those women in the other subgroups.<sup>17,52</sup>

In addition to weight gain, androgenicity and serum adiponectin levels, as outlined earlier, and many other factors may also influence the severity of insulin resistance and overall metabolic dysfunction in women with PCOS:

### 1.2.1 | Adipokines

Adipokines, by definition, are cytokines secreted by adipose tissue. Accordingly, serum levels of adipokines usually associate with body fat mass and severity of obesity. Many adipokines influence insulin sensitivity and overall cardiometabolic risk. One such adipokine, visfatin, plays a role in pathways that involve metabolism, inflammation and insulin sensitivity.<sup>44,53</sup> Serum levels of visfatin are higher in women with PCOS than in control women.<sup>53-56</sup> Elevated levels of serum visfatin in PCOS may therefore contribute towards insulin

resistance and metabolic dysfunction. Reports on other adipokines in PCOS from the literature have produced mixed results. It is possible that retinol binding protein 4 mediates some effects of increased body fat mass on the development of PCOS through effects on insulin sensitivity.<sup>37,57</sup> However, adipocyte fatty acid-binding protein does not appear to associate with either the metabolic or hyperandrogenic features of PCOS.<sup>58</sup> In future studies, it may be helpful to focus on the underlying mechanisms that mediate the effects of serum adipokines on the PI3-K post-receptor insulin pathway in PCOS, and the subsequent development of this condition.

### 1.2.2 | Obstructive sleep apnoea (OSA)

OSA is another obesity-related condition,<sup>59</sup> characterized by recurrent episodes of upper airway obstruction and intermittent hypoxia during sleep, with consequent impairment in sleep quality.<sup>60</sup> Similarly to PCOS, OSA also associates independently with insulin resistance even following adjustments for BMI,<sup>31-33,61</sup> possibly mediated via associated changes in serum adipokines, catecholamines and cortisol.<sup>62</sup>

Although, overall, OSA occurs more commonly in men,<sup>63</sup> women with PCOS are also at greater risk of developing OSA compared with BMI- and age-matched control women.<sup>64</sup> Women with PCOS have a 2-fold higher risk of developing OSA compared to women without PCOS matched for BMI and age, based on data from a large longitudinal study.<sup>65</sup> It is possible that mediation of such an increased risk of OSA in PCOS occurs through the typical hormonal changes of PCOS. For example, testosterone influences apnoeic threshold and breathing instability during sleep.<sup>66</sup> Furthermore, a relative

lack of serum progesterone in anovulatory PCOS<sup>3</sup> may predispose to increased upper airway resistance through reducing the activity of the upper airway dilator muscles.<sup>67</sup> Finally, obesity (particularly visceral fat content) contributes towards the risk of OSA in women with PCOS.<sup>68,69</sup> Due to the combined independent associations between obesity, PCOS and OSA with insulin resistance and metabolic dysfunction, it is perhaps not surprising that obese women with both PCOS and OSA have marked insulin resistance, and a particularly high risk of developing T2D and metabolic syndrome.<sup>70</sup> Based on the evidence outlined here, it is important to screen proactively for OSA (eg. through Epworth questionnaires) at least yearly in obese women with PCOS, given the increased risk of OSA in this population group, its implications for metabolic health, its treatability through weight loss strategies and the application of continuous positive airways pressure (CPAP) therapy.

### 1.2.3 | Visceral and hepatic fat

Mediation of the association between weight gain and insulin resistance occurs primarily through increased amounts of visceral and hepatic fat.<sup>71</sup> Similarly, it is likely that in women with PCOS, there is enhancement of insulin resistance and metabolic dysfunction through visceral and hepatic fat. NAFLD occurs commonly in obese women with PCOS, supporting a role for hepatic fat.<sup>72</sup> This also promotes regular monitoring of liver function through biochemical and/or radiological techniques in obese women with PCOS. However, the role of visceral fat in PCOS is more contentious. Although early studies, using techniques such as ultrasound, suggested a preponderance of visceral fat in women with PCOS, more recently studies have utilized magnetic resonance imaging (MRI) and cast doubt on this hypothesis. We used MRI to compare visceral fat depots (measured through axial cross-sectional areas) between BMI- and fat mass-matched pairs of women with PCOS and controls, and demonstrated equivalent visceral areas between the two groups, despite differences in insulin sensitivity.<sup>69</sup> Subsequent MRI-based studies provided confirmative data.<sup>73,74</sup> However, a lack of visceral fat preponderance in PCOS in no way diminishes the importance of visceral fat as a contributor to insulin resistance in this condition, due to a positive correlation between total body and visceral fat mass depots in women, regardless of their PCOS status.<sup>44,69,75</sup> Therefore, increased volume of visceral fat, associated with overall weight gain and obesity, is likely to contribute to insulin resistance and metabolic dysfunction in PCOS.

## 1.3 | The role of weight gain in the pathogenesis of hyperandrogenism in PCOS

Hyperandrogenism in PCOS encompasses clinical and/or biochemical features. Most commonly, the clinical manifestations of hyperandrogenism include hirsutism, acne and androgenic alopecia. Biochemically, hyperandrogenaemia of PCOS stems from

over-production of androgens, principally from the ovary but with a variable contribution from adrenal glands. It includes raised plasma levels of total testosterone, androstenedione and dehydroepiandrosterone sulphate (DHEAS). In addition, a raised free androgen index also typifies PCOS, resulting from suppression of sex hormone binding globulin (SHBG) in the presence of raised or normal plasma levels of testosterone. Compensatory hyperinsulinaemia in PCOS, through its stimulatory effects on the fully functional post-receptor MAP-K insulin pathway, plays an important role in the establishment of hyperandrogenaemia that in turn underlies the clinical features of hyperandrogenism, with multiple pathogenic pathways implicated:

### 1.3.1 | Stimulatory effects of insulin on the ovarian theca cell – insulin as a co-gonadotrophin

Insulin acts directly as a gonadotrophin within the ovarian theca cells, thereby driving ovarian steroidogenesis through the hyperinsulinaemic effects on the MAP-K insulin pathway. Within the ovarian theca cells, there is synergism of insulin with luteinizing hormone (LH) through the activation of cytochrome P450 17 $\alpha$  (CYP17 or P450c17 $\alpha$ ), a key enzyme in ovarian androgen biosynthesis.<sup>76-78</sup> Ovarian androgen biosynthesis in PCOS may be further enhanced through suppressed levels of serum adiponectin,<sup>36,44</sup> given the known inhibitory effects of adiponectin on ovarian androgen production.<sup>79</sup> In support of this hypothesis, a study in pubertal girls with type 1 diabetes mellitus showed an inverse correlation between levels of serum adiponectin and testosterone and ovarian volume.<sup>80</sup>

### 1.3.2 | Stimulatory effects of insulin on the adrenal cortex

Insulin stimulates steroidogenesis within the adrenal cortex,<sup>3</sup> mediated through effects on adrenal P450c17 $\alpha$  activity.<sup>81</sup> This drives the production of adrenal androgens, including androstenedione and DHEAS that complements the hyperandrogenic effects of enhanced ovarian biosynthesis.

### 1.3.3 | Suppressive effects of insulin on hepatic production of sex hormone binding globulin (SHBG)

Insulin suppresses the hepatic production of SHBG,<sup>82,83</sup> thereby accounting for suppressed serum levels of SHBG in PCOS. A decrease in serum SHBG levels leads to a commensurate increase in the free androgen index (a measure of free, or 'biologically available' androgens), and therefore overall androgenicity. In a recent systematic review and meta-analysis of the literature, it was concluded that serum levels of SHBG may provide a useful biomarker in the management of PCOS,<sup>84</sup> particularly in the assessment of metabolic status. Indeed, suppressed serum levels of SHBG associate with a less favourable cardiovascular disease risk profile, albeit in men.<sup>85</sup>

### 1.3.4 | Stimulatory effects of insulin on the pituitary release of LH

Rodent-based *in vitro* models have demonstrated stimulatory effects of insulin at the level of the pituitary gonadotrophin-releasing cells, with enhancement of the LH pulse amplitude.<sup>32,86</sup> However, the pituitary effects of hyperinsulinaemia in PCOS remain contentious. In one study, it was demonstrated that in women with PCOS, serum LH levels, LH pulse frequency and amplitude and gonadotrophin response to gonadotrophin-releasing hormone (GnRH) were not influenced by the administration of pioglitazone (an insulin-sensitizing drug), either with or without a concurrent infusion of insulin, casting doubt on an important role of hyperinsulinaemia on LH release in PCOS.<sup>87</sup>

Weight gain also drives hyperandrogenaemia in women with PCOS through mechanisms that do not directly implicate hyperinsulinaemia or insulin resistance. In a large study of urinary steroid profiles in PCOS (PCOS:  $n = 178$ ; BMI-matched control women:  $n = 100$ ), an association between PCOS status and enhanced 5- $\alpha$  reductase activity was found.<sup>88</sup> In this study, 5- $\alpha$  reductase activity was also associated with adiposity in both groups,<sup>88</sup> possibly through increased enzyme expression within adipose tissue, although there may be other explanations given that 5- $\alpha$  reductase is expressed in multiple tissues, including in the dermis.<sup>89</sup> We hypothesize that enhanced 5- $\alpha$  reductase activity in women with PCOS drives hyperandrogenaemia through two main mechanisms. Firstly, increased 5- $\alpha$  reductase activity enhances the conversion of cortisol into its breakdown products with associated reduction in the negative feedback effect of cortisol at the hypothalamo-pituitary unit, and consequent activation of the hypothalamo-pituitary adrenal (HPA) axis and further enhancement of adrenal androgen biosynthesis. (To corroborate this hypothesis, our data indeed confirmed enhanced HPA axis activity in women with PCOS compared with BMI-matched control women<sup>88</sup>). Secondly, increased 5- $\alpha$  reductase activity also enhances the conversion of testosterone into the more potent androgen, 5-dihydroxytestosterone (5-DHT). The 5- $\alpha$  reductase driven increased biosynthesis of 5-DHT may therefore further enhance the hyperandrogenic features of PCOS.

### 1.4 | The role of weight gain in the pathogenesis of reproductive dysfunction in PCOS

The reproductive features of PCOS consist primarily of oligo-amenorrhoea and impaired fertility. Underlying these clinical manifestations is abnormal ovarian follicle development leading to infrequent or absent ovulation.<sup>48,90</sup>

Hyperinsulinaemia in PCOS contributes to premature granulosa cell luteinization.<sup>91,92</sup> This combined with enhanced ovarian androgen production results in subsequent arrest of cell proliferation and follicular growth.<sup>90</sup> Furthermore, small antral follicles in PCOS over-express LH receptors,<sup>93,94</sup> and steroid production shifts towards a preponderance of progesterone (rather than estradiol).<sup>90,91</sup> These complex underlying mechanisms translate into arrest of follicle development in PCOS at the pre-antral phase,<sup>48,94,95</sup> that in turn

manifest in oligo-anovulation, oligo-amenorrhoea and impaired fertility. Further rodent-based evidence for an important role of hyperinsulinaemia in impaired follicular development stems from the observation of upregulation of LH receptor expression in cultured mouse cumulus-oocyte complexes with reduced blastocyst development, in response to exposure to insulin and follicle stimulating hormone (FSH).<sup>90,96</sup> Interestingly, there may also be a role for increased intra-ovarian 5- $\alpha$ -reductase activity in PCOS in the pathogenesis of reproductive dysfunction, given the inhibitory effects of 5-DHT on granulosa cell aromatase activity, and subsequent harmful effects of limited estradiol production on oocytes.<sup>90,97,98</sup>

Having explored the mechanisms whereby weight gain and obesity contribute to the pathogenesis of PCOS from the perspective of its three cardinal features of metabolic dysfunction, hyperandrogenism and reproductive dysfunction, including the central role of the insulin pathway (summarized in Figure 2), we now turn to some key aspects of management of PCOS.

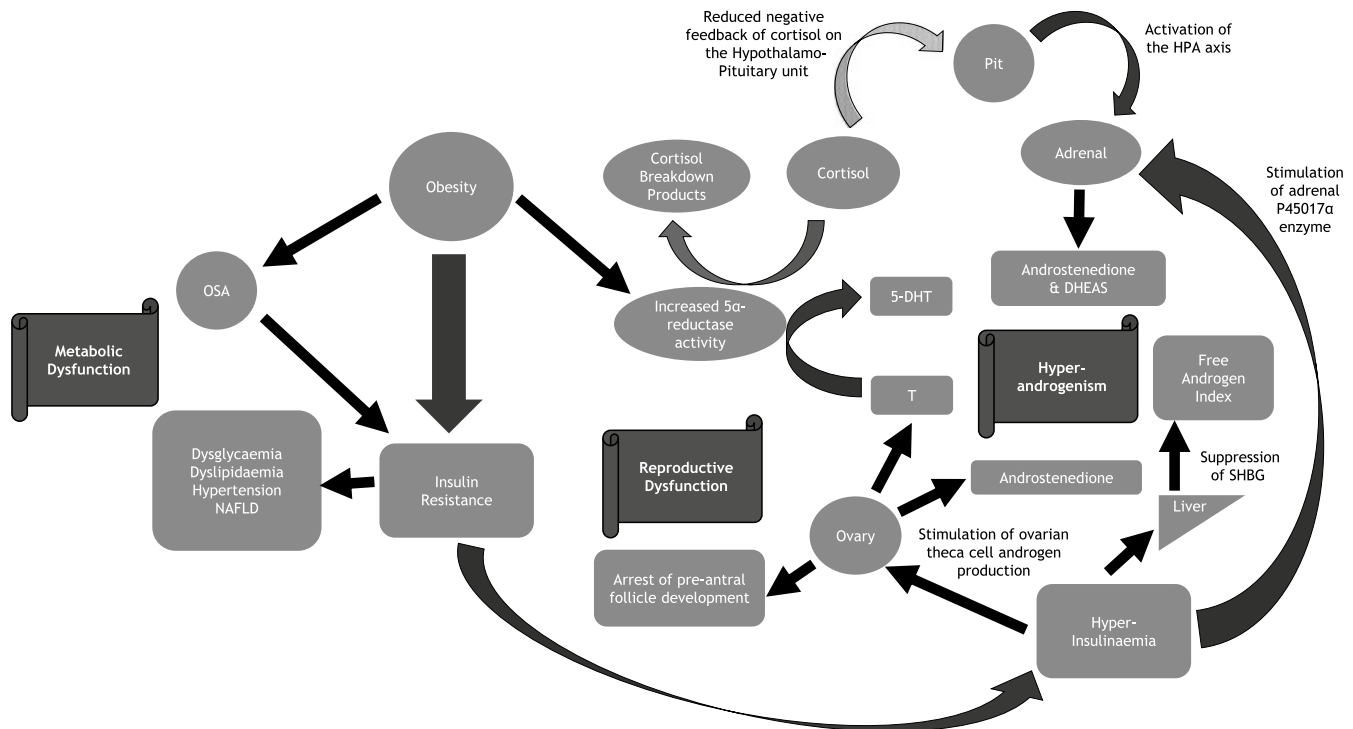
### 1.5 | The role of lifestyle modification in the effective management of PCOS

Given the central role of the dysfunctional insulin signalling in the pathogenesis of PCOS, it is perhaps not surprising that the most effective management strategies for this condition include attempts to improve function of this pathway, including most notably through effective and sustained weight loss. Calorie restriction and weight loss result in a reduction of hyperinsulinaemia and improvement in the hyperandrogenic and reproductive features of PCOS. Indeed, even modest weight loss of around 5% can result in clinically meaningful improvements in the metabolic, hyperandrogenic and reproductive features of PCOS (including restoration of ovulation, menstrual cyclicity and fertility).<sup>3,99-101</sup>

It is beyond the scope of this concise review to provide an exhaustive exposition of the pharmacological management of PCOS, covered in detail elsewhere.<sup>102</sup> Here we focus on lifestyle management strategies, with great potential for improving the clinical outcome for women and girls with PCOS.

#### 1.5.1 | Physical exercise

Regardless of PCOS status or degree of insulin resistance, physical exercise improves insulin sensitivity.<sup>103</sup> Furthermore, physical training, through optimization of glucose transport and metabolism, potentiates the effects of physical exercise on insulin sensitivity.<sup>103</sup> Therefore, engagement in regular physical exercise, regardless of PCOS status, reduces overall cardiovascular risk. This is particularly desirable in obese women with PCOS given the frequent prominence of both metabolic dysfunction and inherent insulin resistance. Optimized physical activity often complements dietary change as an effective means of weight loss through lifestyle change. Importantly however, the beneficial effects of physical activity on insulin



**FIGURE 2** Overview of the role of obesity and insulin resistance in the pathogenesis of PCOS. 5-DHT, 5-Dihydroxytestosterone; DHEAS, Dehydroepiandrosterone sulphate; HPA, Hypothalamo-pituitary adrenal; NAFLD, Non-alcoholic fatty liver disease; OSA, Obstructive Sleep Apnoea; Pit, Pituitary gland; SHBG, Sex Hormone Binding Globulin; T, Testosterone

sensitivity often stem from the activity itself (and combined avoidance of sedentariness), rather than necessarily resulting from any attendant weight loss, (although any resultant weight loss would be expected to further improve insulin sensitivity).

In women with PCOS, aerobic exercise can also improve reproductive function, including normalized menstrual cyclicity<sup>104,105</sup> and ovulation.<sup>105,106</sup> However, despite the clear benefits of physical activity and exercise on reproductive function in women with PCOS, one caveat is that excessive exercise can have the opposite effect. Published data suggest that engagement in physical exercise for >60 minutes per day in women with PCOS can actually increase the risk of anovulation.<sup>107</sup> Conversely, engagement in physical exercise for 30–60 minutes per day reduces the risk of anovulatory infertility.<sup>107</sup> Therefore, as a means of improving insulin sensitivity, reproductive health and overall metabolic health, women with PCOS should be encouraged to engage in regular physical exercise for between 30–60 minutes per day, but to avoid excessive exercise. Finally, it is important to emphasize the importance of physical activity as a means of reducing sedentariness, given the association of the latter with poorer overall metabolic health, cardiorespiratory fitness and liver fat.<sup>108</sup>

### 1.5.2 | Dietary modification

Dietary modification forms a key component of lifestyle implementation for successful weight loss. However, there remains much controversy and incomplete understanding regarding the details of optimal dietary change for the achievement of weight loss in any

scenario. In a recent review of the literature on the effects of dietary modification on weight loss, there was no evidence to support any single dietary scheme (including food group, nutrient or dietary pattern) as being more efficacious than other options.<sup>109</sup> There was also an identified gap in the literature regarding the effect of dietary modifications on weight maintenance, with most studies reporting the effects of weight loss regimes.<sup>109</sup>

In women with PCOS, it is important to advocate the adoption of a healthy and balanced diet to optimize overall health and wellbeing, although dietary modification is often encouraged to achieve weight loss. Unfortunately, as with diets in general, there is contention regarding the optimal dietary composition to facilitate weight loss in obese women with PCOS. A comprehensive review of the literature on the weight-losing effects of various diets revealed subtle differences.<sup>110</sup> Monounsaturated fat-enriched and low-glycaemic index diets are associated with greater weight loss and improved menstrual regularity, respectively.<sup>110</sup> Furthermore, low-carbohydrate or low-glycaemic index diets are associated with greater reductions in insulin resistance and an improvement in lipid profile.<sup>110</sup> A high-protein diet is associated with reduced depression and improved self-esteem. Finally, high-carbohydrate diets are linked with increased free androgen index.<sup>110</sup> Therefore, based on the available evidence, perhaps the best dietary advice we can provide obese women with PCOS is to reduce their overall caloric intake, whilst maintaining a healthy, balanced and nutritionally replete diet. Use of low-carbohydrate or low-glycaemic index diets appears particularly helpful, whilst maintaining high intake of protein. Finally, a diet rich in dietary fibre can also contribute towards successful weight loss, in

addition to conferring numerous other health benefits through the establishment and nurture of a diverse gut microbiota.<sup>111</sup>

### 1.5.3 | Optimization of sleep

It is hard to overstate the importance of sleep for normal physiological functioning. Sleep deprivation adversely affects nearly every aspect of mental and emotional functioning, and impacts negatively on physiology generally, including promotion of metabolic dysfunction, inflammation and importantly, insulin resistance.<sup>112</sup> In addition to being an independent risk factor for insulin resistance, sleep deprivation also associates with increased BMI<sup>113</sup> and results in changes to appetite and increased caloric ingestion. In one study, sleep deprivation for just 2 nights resulted in enhanced appetite and increased caloric ingestion, with a preference for sweet and fatty foods. There were also changes in serum levels of the appetite hormones, including ghrelin (increased) and leptin (decreased).<sup>114,115</sup>

The strong association between PCOS and OSA, mediated through effects on insulin resistance,<sup>64</sup> provides a rationale for exploring the effects of treatment of OSA on the clinical features of PCOS. Indeed, one study explored the effects of treatment with CPAP therapy in a cohort of women with PCOS and OSA demonstrating that this therapy was effective at alleviating insulin resistance, and partially reversed metabolic dysfunction.<sup>116</sup> Furthermore, bariatric surgery is an excellent treatment option for OSA, with a resolution rate of 85% based on a large systematic review of the literature.<sup>117</sup> Key learning points from the literature include improved awareness of the strong link between PCOS and OSA, and the independent effect of OSA on insulin resistance and the severity of the clinical and metabolic features of PCOS. Therefore, we should adopt a proactive approach to screening for OSA in obese women with PCOS. Screening for OSA should form an annual assessment in obese women with PCOS, and we should have a low threshold for requesting polysomnography and focused sleep assessment once there is a clinical suspicion of OSA. A diagnosis of OSA promotes candidacy for bariatric surgery in obese women with PCOS, given the confirmed efficacy of this treatment modality. Finally, OSA in women with PCOS often requires effective treatment with CPAP therapy from specialist teams.

In addition to the effective diagnosis and management of OSA in obese women with PCOS, it is also important to ensure optimization of sleep sufficiency. The success of implemented lifestyle measures (including dietary modification) to lose weight appear to depend on a prerequisite of sleep sufficiency.<sup>118</sup> In one study, a 2-week intervention of individualized counselling on sleep hygiene in overweight participants enabled a sleep duration of 7-8 hours per night (compared with their usual pre-study <6.5 hours of sleep per night). This intervention resulted in a 14% reduction in overall appetite ratings (particularly for sweet and salty foods), a 7% increase in daytime activity and improved sleepiness.<sup>119</sup> Based on such evidence, sleep sufficiency forms a pillar of lifestyle management for obesity, particularly in women with PCOS. The ability to modify one's diet and engage in physical activity depends on adequate sleep. Conversely,

sleep deprivation hinders attempts to lose weight through lifestyle measures,<sup>120</sup> including adverse effects on appetite and overall wellbeing. Rather than being an 'afterthought' or even overlooked entirely, a focus on sleep sufficiency should be prioritized before instituting other lifestyle measures such as dietary change.

To optimize sleep duration, there are useful strategies that include avoidance of blue light from screens during late evening, to allow natural melatonin release and the onset of sleepiness.<sup>121</sup> Furthermore, it is necessary for the body to cool prior to sleep, therefore ensuring a cool bedroom is important. A focus on daily routines is also important, with avoidance of food and exercise in the hour before sleep, and ensuring physical activity during the day can also facilitate restful sleep.<sup>122</sup> Finally, to improve sleep sufficiency on a population level will require some degree of cultural and societal change. This includes a collective re-discovery and appreciation for the value and importance of sleep for our overall health, productivity and wellbeing.

### 1.5.4 | Mindfulness

Mindfulness is a state of being that enables a heightened awareness of one's own internal emotions and immediate environs.<sup>123</sup> Ultimately, effective lifestyle change requires modified behaviour that in turn depends on mind-set and emotions. Although application of mindfulness techniques could apply to any lifestyle measure, dietary change (including eating-related behaviour) is especially relevant. Multiple non-appetite-related factors influence our modern-day eating-related behaviour, including social norms and expectations, abundant food availability, food addiction and habitualized meal times.<sup>124,125</sup> Therefore, there is certainly a need to apply mindfulness techniques to eating-related behaviour.<sup>126</sup>

Our own group demonstrated proof of concept that application of mindfulness techniques (taught in groups as part of a hospital-based obesity management service) enables effective weight loss and adoption of healthy eating behaviours.<sup>123</sup> Although this study did not focus exclusively on women with PCOS, there seems no reason why our proof of concept data would not also apply to obese women with PCOS. This should be a focus for future research. In a further study, application of mindfulness techniques to overweight and obese participants also resulted in improved impulsive and binge eating behaviours with an additional benefit of improved physical activity, although interestingly no effects on body weight.<sup>127</sup> Finally, Shomaker and colleagues explored the implementation of a mindfulness-based intervention (MBI) compared to cognitive-behavioural therapy (CBT) in overweight and obese adolescent girls with symptoms of depression and at risk for the development of T2D. There were significant improvements in insulin resistance and depression in those girls randomized to MBI compared to those who received CBT. Given the similarity of this cohort to obese adolescent girls who develop PCOS, these data support a potential role for MBIs as a management strategy for PCOS.

There are many potential applications of mindfulness to the clinical management of PCOS. This includes the development and



maintenance of healthy lifestyle choices (including diet), but also as an expedient towards the establishment and maintenance of mental and emotional wellbeing, in the context of reproductive (including fertility) and hyperandrogenic disturbances. There are also many ways to teach our patients mindfulness techniques. Although formal one-to-one training in mindfulness may be beyond the remit of many healthcare settings currently within the NHS, virtual training sessions for mindfulness are possible in the future. Furthermore, there are many opportunities for patients to self-teach mindfulness techniques through various digital applications.

## 2 | CONCLUSION

As the obesity epidemic ensues, and the global population continues to rise, it is likely that the prevalence of PCOS will also increase in the future. Given our genetic propensity for weight gain, and for the development of PCOS in some women, there seem to be two broad strategies on which to focus for the future prevention and management of PCOS: i) to change our genes (or, rather, modify gene expression); ii) to change our behaviour. A future potential strategy exists to manipulate, therapeutically, the expression of those genes that underlie a propensity for the development of PCOS, including, for example, through epigenetic modification. Studies in animal models reveal that epigenetic changes may play a key role in mediating the effects of lifestyle modification through dietary change, physical activity, attention to sleep quality and sufficiency and application of techniques such as mindfulness. In our modern-day, busy, stressful, distracting and obesogenic environment, there is still much progress required in the development and successful application of lifestyle changes in women with PCOS, ultimately to facilitate effective loss and maintenance of body weight, but also to provide a basis on which to develop emotional wellbeing.

From the vantage point of dysfunctional insulin signalling, we can think of PCOS as a metabolic disorder. This perspective also provides a clear view of the role of weight gain and obesity in the pathogenesis of PCOS, through its effects on worsening aberrant insulin signalling by the PI3-K post-receptor pathway. Furthermore, the resultant compensatory hyperinsulinaemia, and its effects on the functional MAP-K post-receptor insulin pathway, provides an explanation for the subsequent emergence of hyperandrogenism and reproductive dysfunction. The key role of abnormal insulin signalling provides insight into the central role of weight loss, and other factors that influence insulin sensitivity (such as improved sleep quality and sufficiency) in the effective management of women with PCOS.

Finally, having focused primarily on the complex pathogenic pathways that link weight gain and obesity with PCOS, we should never lose sight of the patient at the centre. Obesity is highly stigmatized in our society. Hirsutism, acne and sub-fertility challenge key attributes of womanhood. The frequent clinical manifestation of PCOS during adolescence, a stage of life during which identity develops and vulnerability is prominent, only serves to heighten the potential for a negative impact of PCOS on the patient. Women and

girls with obesity and PCOS require careful clinical management, administered with a compassionate and empathic approach, ideally from a multi-disciplinary specialist team, and with the patient placed at centre-stage.

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## CONFLICT OF INTEREST

None of the authors has any conflict of interest.

## AUTHOR CONTRIBUTION

Both authors contributed substantively to the preparation of this manuscript.

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