

Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; a comprehensive review of clinical interactions and underlying pathophysiology

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DOI:

[10.1111/cen.13392](https://doi.org/10.1111/cen.13392)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Kahal, H, Kyrou, I, Tahrani, AA & Randeve, HS 2017, 'Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; a comprehensive review of clinical interactions and underlying pathophysiology', *Clinical Endocrinology*. <https://doi.org/10.1111/cen.13392>

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Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; a comprehensive review of clinical interactions and underlying pathophysiology.

Journal:	<i>Clinical Endocrinology</i>
Manuscript ID	CEN-2017-000282.R1
Manuscript Type:	5 Unsolicited Review
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Kahal, Hassan; University of Warwick Warwick Medical School, Division of Translational and Experimental Medicine; University Hospitals Coventry and Warwickshire NHS Trust, Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM)</p> <p>Kyrou, Ioannis ; University of Warwick Warwick Medical School, Division of Translational and Experimental Medicine; University Hospitals Coventry and Warwickshire NHS Trust, Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM); Aston University, Aston Medical Research Institute, Aston Medical School,</p> <p>Tahrani, Abd; University of Birmingham, Institute of Metabolism and Systems Research, School of Clinical and Experimental Medicine; University of Birmingham, Centre of Endocrinology, Diabetes and Metabolism (CEDAM); Birmingham Heartlands Hospital, Department of Diabetes</p> <p>Randeva, Harpal; University of Warwick Warwick Medical School, Division of Translational and Experimental Medicine; University Hospitals Coventry and Warwickshire NHS Trust, Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM); Aston University, Aston Medical Research Institute, Aston Medical School,</p>
Key Words:	Polycystic ovary syndrome < Conditions: < Ovary, Obstructive sleep apnoea, Obesity, morbid < Conditions: < Obesity/Lipids/Nutrition, Hyperandrogenism, Insulin resistance < Conditions: < Pancreas

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3 1 **Title: Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; a comprehensive**
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5 2 **review of clinical interactions and underlying pathophysiology.**
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46 17 **Key words:** Polycystic ovary syndrome; PCOS; Obstructive Sleep Apnoea; OSA;
47
48 18 Hyperandrogenism; Obesity; Insulin Resistance.
49

50
51 19 Manuscript: 3214 words (excluding abstract, tables, and figures). Number of Tables: 1.
52

53 20 Number of Figures: 1. Abstract: 153 words. References: 58.
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10 25 **Declaration of interest:** The authors declare that there is no conflict of interest that could be
11
12 26 perceived as prejudicing the impartiality of the paper reported. No funding was received for
13
14 27 doing this work. Dr Abd Tahrani is a Clinician Scientist supported by the National Institute
15
16 28 for Health Research. The views expressed in this publication are those of the author(s) and
17
18 29 not necessarily those of the NHS, the National Institute for Health Research or the
19
20 30 Department of Health. NIHR Clinical Lectureship supported Dr. Hassan Kahal. All authors
21
22 31 reviewed and edited the manuscript and approved the final version of the manuscript.
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34 **Abstract**

35 Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in women of
36 reproductive age. PCOS is associated with multiple co-morbidities including, obesity, insulin
37 resistance and type 2 diabetes, as well as mood disorders and impaired quality of life (QoL).
38 Obstructive sleep apnoea (OSA) is also a common medical condition that is often
39 undiagnosed, particularly in women. OSA is associated with a similar spectrum of
40 comorbidities to that observed in PCOS, including manifestations of the metabolic syndrome
41 and impaired QoL, whilst obesity frequently constitutes a common denominator in the
42 pathophysiology of both OSA and PCOS. Hence, it is not surprising that OSA and PCOS
43 may co-exist in women of reproductive age, and the current clinical guidelines on the
44 management of PCOS recommend screening for OSA symptoms in overweight/obese women
45 with PCOS. In this review, we examine the relationship between OSA and PCOS and explore
46 the potential underlying mechanisms that link these two conditions.

47

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common **endocrine** disorder in women of reproductive age with a prevalence of 6–15% (3, 4). PCOS is associated with obesity, subfertility, insulin resistance (IR) and type 2 diabetes (T2DM), depression and impaired quality of life (QoL) (1, 5). **However, despite its high prevalence and significant comorbidities, our understanding of its underlying pathophysiology remains poor; with limited treatment options available to manage this lifelong disorder in everyday clinical practice.**

Hence, there is a need to improve the understanding of the pathogenesis of PCOS and the spectrum of factors that might contribute to the clinical manifestations and comorbidities of this very common condition.

Obstructive sleep apnoea (OSA) is also an obesity-related disorder. OSA prevalence in the general population is estimated at 17–26% in men and 9–28% in women, but this difference varies depending on the definition and methods used to diagnose OSA (6). OSA is characterised by recurrent episodes of partial (hypopnoea) or complete (apnoea) upper airway obstructions associated with recurrent oxygen desaturations and cyclical changes in heart rate, blood pressure, intrathoracic pressure and sympathetic activity (7). In addition, OSA results in changes in the sleep architecture, including loss of deep sleep (stages 3 and 4) and/or of REM sleep (7).

Patients with OSA may present with nocturnal symptoms, including snoring, witnessed apnoea episodes, choking or gasping, insomnia, nocturia, enuresis, frequent arousals, diaphoresis, and impotence (8). In addition, common daytime OSA symptoms may include excessive daytime sleepiness, fatigue, memory impairment, morning headaches, and depression (8). Prompt diagnosis and treatment of OSA is highly important in clinical practice, since undiagnosed/untreated OSA is associated with increased risk of hypertension,

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3 72 cardiovascular disease, mortality, IR and T2DM, road traffic accidents, depression and
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5 73 impaired QoL (8, 9) . Continuous positive airway pressure (CPAP) therapy, combined with
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7 74 weight loss for overweight/obese patients, is the treatment of choice for symptomatic OSA
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9 75 (10).

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12 76 Despite the high prevalence of OSA in the general population, this condition is generally
13
14 77 under-recognised and frequently remains undiagnosed in everyday clinical practice,
15
16 78 particularly in women who may not present with typical OSA symptoms (11). As obesity is a
17
18 79 common risk factor, it is not surprising that OSA and PCOS might co-exist. **The association**
19
20 80 **between PCOS and OSA has also been recognised in the latest guidelines by the European**
21
22 81 **and the US Endocrine Societies (Box 1) (1, 2). However, these guidelines acknowledge the**
23
24 82 **limited evidence behind their recommendations that is largely based on limited, ‘weak’, or**
25
26 83 **‘low quality’ data. This highlights the need for further research to better understand the**
27
28 84 **relationship between PCOS and OSA. In addition,** the implications of OSA in women with
29
30 85 PCOS are not clear, though important as both conditions are associated with overlapping
31
32 86 comorbidities, and OSA is associated with essential factors that may contribute to the burden
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34 87 of PCOS (*e.g.* to IR, increased inflammation, and oxidative stress) (6, 12). In this article we
35
36 88 present a concise review of key studies that examined the relationship between OSA and
37
38 89 PCOS, and we explore the potential mechanisms linking both conditions.

44
45 **Box 1. Clinical guidelines/recommendations on screening women with PCOS for OSA.**

46
47 1. Endocrine Society, 2013 (1):

48 We suggest screening overweight/obese adolescents and women with PCOS for symptoms
49 suggestive of OSA and, when identified, obtaining a definitive diagnosis using
50 polysomnography. If OSA is diagnosed, patients should be referred for institution of
51 appropriate treatment.

52
53 2. European Society of Endocrinology, 2014 (2):

54 It seems wise at this moment to screen sleep disorders by clinical questionnaires in obese
55 women with PCOS. In the case of clinical suspicion resulting from these questionnaires,
56 patients should be referred to a centre of sleep disorders for polysomnography and further
57 evaluation.

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91 **2. Methodology**

92 We conducted a narrative review of the relevant literature. In this context, we searched
93 PubMed using the terms '(PCOS OR polycystic ovary syndrome) AND (OSA OR obstructive
94 sleep apnoea OR obstructive sleep apnea)'. Clinical studies and review articles examining the
95 presence of OSA in women with PCOS were obtained, reviewed, and their results were
96 critically appraised. We also hand-searched references from relevant papers and review
97 articles.

98 **3. Epidemiology**

99 **3.1 PCOS prevalence in OSA**

100 PCOS has a prevalence of 6–15% in women of reproductive age (3); however, the reported
101 prevalence rates vary depending on the populations studied and the applied PCOS diagnostic
102 criteria. The prevalence of PCOS in women with OSA remains unknown.

103

104 **3.2 OSA prevalence in PCOS**

105 The prevalence of OSA in the general population varies considerably between studies, mainly
106 due to differences in the populations studied, study designs, and the methods and criteria used
107 to diagnose OSA (8). The prevalence from three well-conducted studies with similar designs
108 from the USA (Wisconsin and Pennsylvania), and Spain showed an OSA prevalence of 9–
109 28% in women, with 2–7% for moderate to severe OSA (13).

110 To date, a limited number of studies have examined the prevalence of OSA in women with
111 PCOS with the majority of these being conducted in the USA. Based on the existing
112 published studies (14-22) (Table 1), the reported prevalence of OSA in women with PCOS

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3 113 ranges from 0% to 69% (median: 55.8%; mean: 39.8%). This large variability and wide range
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5 114 in the reported prevalence may be attributed to a combination of reasons, including
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7 115 application of different cut-off points and methods to diagnose OSA, the small size of the
8
9 116 studied cohorts, and potential selection bias by recruitment of study participants from
10
11 117 specialised clinics. As expected, the available data suggest that OSA risk in women with
12
13 118 PCOS is increased with age and obesity. While the only published study that examined the
14
15 119 presence OSA in lean women with PCOS showed no evidence of the condition (18), the
16
17 120 small number of study participants (n=18) precludes generalisability or drawing firm
18
19 121 conclusions from these data. The reported prevalence and potential links between PCOS and
20
21 122 OSA in adolescents are even more controversial, with one study showing a prevalence of
22
23 123 16/28 (57%) (20) and another showing 0/22 (0%) prevalence (19). Based on the available
24
25 124 data on the prevalence and natural history of these two conditions, it is probable that PCOS
26
27 125 precedes the development of OSA; however, it cannot be excluded that OSA may precede the
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29 126 clinical presentation of PCOS in some women, worsening the PCOS-related
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31 127 symptomatology. Observational long-term studies are needed to accurately assess the
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33 128 incidence of OSA in women with PCOS and *vice versa*.

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130 **4. Proposed mechanisms linking OSA to PCOS and its comorbidities**

131 **Depending on ethnicity and geography, 30–88% of women with PCOS are overweight or**
132 **obese (23). Obesity may contribute to the development of PCOS through increased android**
133 **(central) type adiposity and IR (24); lipotoxicity (25); and increased 5 α -reductase activity**
134 **(23). Obesity is also a major risk factor for OSA (8). The mechanisms that link obesity to**
135 **OSA are multifactorial (8, 26). Weight gain can alter normal upper airway mechanics during**
136 **sleep by various mechanisms, such as increased parapharyngeal fat deposition resulting in a**

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3 137 smaller upper airway; altering the neural compensatory mechanisms that maintain airway
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5 138 patency; reducing the functional residual capacity with a resultant decrease in the stabilising
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7 139 caudal traction on the upper airway; reducing lung volume due to increased abdominal fat;
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10 140 increasing breathing workload due to increased chest wall thickness; and affecting the
11
12 141 chemosensitivity to O₂ and CO₂ which reduces the ventilatory drive (8, 26). Subsequently,
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14 142 obesity is a key factor that predisposes to both PCOS and OSA. However, other shared
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16 143 features between PCOS and OSA may also play an important mechanistic role in the
17
18 144 development/interaction between these two common conditions.

145 **4.1 Sex Hormones**

146 An increase in circulating androgens of ovarian origin is one of the main features of PCOS
147 and is present in both ovulatory and anovulatory women. Androgens cause many of the
148 clinical features of PCOS (*e.g.* hirsutism, acne and alopecia); contribute to anovulation by
149 promoting ovarian early follicular growth and subsequently disrupt follicular development
150 and dominant follicle selection (27); and exacerbate IR. Anovulation will result in lower
151 progesterone levels. Hyperandrogenism and low progesterone levels may play a role in the
152 pathogenesis of OSA by increasing upper airway collapsibility, and/or impairing the
153 sensitivity and responsiveness of the ventilatory chemoreceptors (28). However, the effect of
154 hyperandrogenism on OSA risk in women with PCOS is probably small, as androgen levels
155 are relatively low compared to men. Sleep, on the other hand, appears to have a significant
156 effect on the female hormone production (29). Indeed, sleep deprivation and/or interruption,
157 and sleep disordered breathing have been suggested to influence gonadotropin releasing
158 hormone (GnRH), follicular stimulating hormone (FSH) and luteinising hormone (LH)
159 pulsatility and may cause menstrual disturbances (30, 31). Subsequently, OSA may alter sex
160 hormones production and contribute to the development or worsening of the clinical features
161 of PCOS.

162 **4.2 Insulin resistance**

163 IR is seen in more than 50% of women with PCOS, independent of obesity (32). Insulin may
164 act directly on the ovaries to enhance androgen production (33); reduce SHBG production
165 from the liver with subsequent increase in bioavailable testosterone; and cause the premature
166 arrest of follicle growth and anovulation (34). Most studies also suggest an association
167 between OSA and IR (8); and studies in healthy lean men found OSA to be associated with
168 IR even in the absence of obesity (35). In addition, in a cohort study, OSA, apnoea/hypopnea
169 index (AHI), oxygen desaturation index (ODI), and minimal oxygen saturations were
170 independently associated with IR development over an 11-year follow-up period after
171 adjustment for age, baseline BMI, BMI change over follow-up, hypertension, and CPAP
172 treatment (36). Two recent meta-analyses showed that CPAP treatment was associated with a
173 reduction in the homeostasis model assessment of insulin resistance (HOMA-IR) (37, 38),
174 although this benefit may occur only in those using CPAP >4 hours per night (39).
175 Subsequently, it is plausible that OSA, through IR, may contribute to the development of a
176 more severe PCOS phenotype in women affected by both conditions; or to a *de novo*
177 presentation of PCOS in genetically/metabolically predisposed women.

178 **4.3 Oxidative stress**

179 In a recent systematic review and meta-analysis, PCOS was associated with increased levels
180 of oxidative stress, independent of age and BMI (40). Oxidative stress may play a role in the
181 pathogenesis of PCOS by exacerbating IR (41); causing hyperandrogenism (41); and
182 contributing to infertility (42). Many studies suggest that OSA is a cause of oxidative stress
183 (8). Recurrent hypoxia and mitochondrial dysfunction in OSA result in the formation of
184 reactive oxygen species (ROS) which leads to cellular and DNA damage and oxidative stress

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3 185 (43). Subsequently, OSA may complicate the clinical picture in PCOS by promoting
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5 186 oxidative stress.
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8 187 **4.4 Endothelial dysfunction**

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11 188 Women with PCOS have been found to have lower flow-mediated dilatation (FMD)
12
13 189 compared to age- and weight-matched controls (44). Obesity, IR, oxidative stress, advanced
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15 190 glycation end products (AGE) and inflammation are believed to play a role in the
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17 191 pathogenesis of endothelial dysfunction in PCOS (45). OSA is also associated with
18
19 192 endothelial dysfunction and the underlying mechanisms are likely related to ischemia-
20
21 193 reperfusion injury (46). Repetitive episodes of re-oxygenation after hypoxemia in patients
22
23 194 with OSA result in increased production of AGE and ROS (43); altered protein kinase C
24
25 195 signaling; decreased endothelial nitric oxide synthase (47); increased endothelin-1 levels and
26
27 196 inflammation (48). Notably, CPAP treatment was found to increase FMD in patients with
28
29 197 OSA (49).
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34 198 **4.5 Sympathetic activity**

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37 199 Sympathetic activity is increased in obesity and is associated with visceral adiposity (50);
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39 200 high leptin levels (51) and IR (52) are thought to play a role in its pathogenesis. However,
40
41 201 increased sympathetic activity may further exacerbate IR and creates a vicious cycle (52).
42
43 202 Women with PCOS have evidence of increased sympathetic activity (52), even in the absence
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45 203 of obesity (53). Sympathetic activity may contribute to the pathogenesis of PCOS through
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47 204 increased IR, altered ovarian function and the development PCO morphology (52). OSA is
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49 205 also associated with an increase in sympathetic activity independent of body weight (54). It is
50
51 206 likely that both the recurrent hypoxia (55) and recurrent arousals (56) contribute to the
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53 207 activation of the sympathetic nervous system (SNS). Moreover, treatment with CPAP is
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55 208 associated with a reduction in sympathetic activity (57).
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209 **4.6 Summary of the proposed mechanisms linking OSA and PCOS**

210 OSA and PCOS are both associated with comorbidities including obesity, IR, oxidative
211 stress, endothelial dysfunction, sympathetic hyperactivity, and hormonal disturbances that
212 could potentially contribute to the pathophysiology and development of either condition. It is
213 thus plausible that the relationship between OSA and PCOS is bidirectional, where PCOS
214 contributes to the development of OSA, and *vice versa*, OSA contributes to the clinical
215 presentation of PCOS, worsening its symptomatology and creating a vicious cycle between
216 the two conditions. An illustration of the possible pathophysiological links between OSA and
217 PCOS and their clinical consequences is provided in Figure 1.

220 **5. The impact of OSA in women with PCOS**

221 **5.1 Review of published studies**

222 A limited number of studies have examined the effect(s) of OSA in women with PCOS and
223 their findings are summarised in Table 1.

224 In the study by Vgontzas *et al.* (15), women with PCOS and sleep disordered breathing (SDB
225 was defined as either OSA or upper airway resistance syndrome; n=9) were heavier (BMI
226 45.7 ± 2.6 vs. 37.2 ± 1.1 kg/m², P<0.003), and had higher fasting insulin (306.5 ± 52.4 vs.
227 176.1 ± 18.5 pmol/L, P<0.01) and lower glucose-to-insulin ratio (0.02 ± 0.006 vs. 0.04 ± 0.003 ,
228 P<0.05) compared to women with PCOS without SDB (n=44). Logistic regression analysis of
229 the study data showed that insulin levels and glucose-to-insulin ratio had a stronger
230 association with SDB than age, BMI, or testosterone levels. **However, the difference in BMI**
231 **between the two groups in this study was rather high (8.5 kg/m²), and despite statistical**

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3 232 adjustment, it is difficult to completely rule out an effect of obesity on the metabolic
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5 233 differences between the two groups.
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8 234 Similarly, in the study by Tasali *et al.* (17), women with PCOS and OSA (n=29) were older
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10 235 (age 31.6±1.0 vs. 27.3±0.7 years; P=0.002), had a higher BMI (42.2±1.1 vs. 35.3±1.4 kg/m² ;
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12 236 P<0.001), and were more insulin resistant (HOMA-IR 5.7±0.4 vs. 3.5±0.4, P=0.006) than
13
14 237 women with PCOS without OSA (n=23). After controlling for age, BMI, and ethnicity, AHI
15
16 238 was a highly significant predictor of the fasting concentrations of glucose and insulin, as well
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18 239 as of the 2-h glucose concentration (after an oral glucose tolerance test) and HOMA-IR. The
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20 240 data of this study also suggest that the degree of sleep fragmentation, rather than the severity
21
22 241 of hypoxia, may be related to the severity of IR and glucose intolerance in women with
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24 242 PCOS. As such, the authors further concluded that women with PCOS and OSA represent a
25
26 243 metabolically different, ‘higher risk’ population compared to women with PCOS without
27
28 244 OSA. However, this conclusion should be taken with caution considering the small study
29
30 245 sample size, and the relatively large difference in BMI (7.1 kg/m²) between women with and
31
32 246 without OSA in this study.
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38 247 Notably, Tasali *et al.* have also conducted a relevant short-term interventional study (58) in
39
40 248 19 obese women with PCOS and OSA (age ± SEM: 31.2±1.2 years; BMI: 46.4±2.4 kg/m²).
41
42 249 These women were treated with CPAP for 8 weeks, exhibiting subsequent improvement in
43
44 250 insulin sensitivity (relative increase of nearly 7%), and reduction in diastolic blood pressure
45
46 251 (DBP; approximately 2.3 mmHg). In addition, day-time and night-time norepinephrine levels
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48 252 also reduced after CPAP therapy. However, this study lacked a control group, and only a ‘per
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50 253 protocol’ analysis was performed including just 9 study participants, with the data from
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52 254 another 10 study patients being excluded from the analysis due to lack of adequate CPAP
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54 255 treatment compliance (average use of CPAP <4 hours per night). Of note, whether the
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3 256 reported post-treatment changes in IR and blood pressure observed in this study may
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5 257 translate/result into meaningful clinical outcomes remains to be studied.
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8 258 In another study by Tock *et al.* (21), women with PCOS and OSA (n=12) had higher BMI
9
10 259 (37.8±4.8 vs. 30.67±7.7 kg/m², P=0.006); waist circumference (114.4±12.0 vs. 98.1±19.9 cm,
11
12 260 P=0.013); waist-to-hip ratio (1.0±0.1 vs. 0.9±0.1, P=0.029); free testosterone (1.9±1.3 vs.
13
14 261 1.1±0.8 ng/dL, P=0.014); HOMA-IR (4.4±3.2 vs. 2.3±1.4, P=0.009); total cholesterol
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16 262 (205.0±28.7 vs. 172.3±35.8 mg/dL, P=0.009); low density lipoprotein-cholesterol (LDL,
17
18 263 128.6±21.6 vs. 98.9±29.6, P=0.004); and higher prevalence of non-alcoholic fatty liver
19
20 264 disease (NAFLD, 83.3% vs. 26.9%, P<0.001) compared to those without OSA (n=26). After
21
22 265 adjusting for obesity in multivariate logistic regression analysis, raised serum free
23
24 266 testosterone levels ≥1.07 ng/dL increased the risk of OSA in women with PCOS by 8.2 fold.
25
26 267 Accordingly, the authors concluded that hyperandrogenism may be a predisposing factor for
27
28 268 OSA in PCOS. However, a limitation of this study is the fact that testosterone was measured
29
30 269 by immunoassay rather than by tandem mass spectrometry. In a subsequent multiple logistic
31
32 270 regression analysis, with OSA (AHI ≥5), IR (HOMA-IR ≥2.7), and obesity (BMI ≥30 kg/m²)
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34 271 considered as independent variables and NAFLD as the dependent variable, only OSA was an
35
36 272 independent predictor of the presence of NAFLD. The presence of OSA increased the chance
37
38 273 of NAFLD 7.6 fold in woman with PCOS. As such, the authors concluded that OSA is a
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40 274 predictor of NAFLD along with, but independent of, obesity and IR.
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46 275 In a recent study by Chatterjee *et al.* (22), women with PCOS and SDB (n=33) had higher
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48 276 BMI (29.8±3.4 vs. 24.36±2.29 kg/m², P<0.001), waist circumference (95.58±6.47 vs.
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50 277 85.12±4.34, P<0.001), systolic BP (SBP, 129.27±10.93 vs. 119.18±8.03 mmHg, P=0.002),
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52 278 diastolic BP (78.61±9.07 vs. 73.53±6.22 mmHg, P=0.044), and hirsutism (Ferriman–Gallwey
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54 279 score 9.82±2.78 vs. 8.00±2.5, P=0.028) compared to women with PCOS without SDB
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3 280 (n=17). Interestingly, in a logistic regression analysis which adjusted for BMI, only the
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5 281 associations between fasting plasma glucose and diastolic BP with SDB remained significant.
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8 282 Finally, in the study by Nandalike *et al.* (20), adolescent girls with PCOS and OSA (n=16)
9
10 283 had higher prevalence of the metabolic syndrome (56.3% vs. 8.3%, P=0.03); higher HOMA-
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12 284 IR >4 (81.3% vs. 41.6%, P=0.03), systolic BP (128.4±12.8 vs. 115.6±11.4 mmHg, P=0.009),
13
14 285 triglycerides (149.7±87.7 vs. 93.3±25.8 mg/dl, P=0.03), and lower high density lipoprotein
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16 286 (HDL, 38.6±8.7 vs. 49±10.9 mg/dl, P=0.01) compared to girls with PCOS without OSA
17
18 287 (n=12).
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24 25 289 **5.2 Summary of the literature**

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27
28 290 It seems plausible that OSA is associated with the severity of the PCOS phenotype,
29
30 291 particularly in overweight/obese and insulin resistant women with PCOS. However, it is
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32 292 difficult to draw firm conclusions from the studies conducted so far since significant
33
34 293 variables (*e.g.* abdominal adiposity and ethnicity) have often not been accounted for in the
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36 294 presented analyses. In addition, while the association between OSA and increased insulin
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38 295 resistance in women with PCOS seems to be a common theme, the relationship between OSA
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40 296 and hyperandrogenism is more controversial and require further evaluation. While the US
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42 297 and European Endocrine societies' guidelines consider the presence of OSA as a
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44 298 cardiovascular risk factor in women with PCOS (1, 2), there is lack of data on the exact
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46 299 relationship between OSA and important clinical outcomes in women with PCOS (*e.g.* on
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48 300 T2DM risk, cardiovascular risk, subfertility, depression, and impaired QoL). Subsequently,
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50 301 well conducted observational studies are needed to examine the effects of OSA in women
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52 302 with PCOS. Interventional studies are also required in women with PCOS and OSA. The
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54 303 existing short-term, pilot, interventional study in such patients suggests that CPAP therapy
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3 304 may significantly improve insulin sensitivity and reduce blood pressure. However, it remains
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5 305 unclear whether this can translate into long-term meaningful clinical outcomes.
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10 11 307 **6. Conclusions** 12

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14 308 OSA appears to be common in obese women with PCOS. There is a lack of high-quality
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16 309 evidence regarding the clinical benefit or the cost-effectiveness of the current Endocrine
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18 310 Society clinical practice guidelines which suggest screening all overweight/obese adolescents
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20 311 and women with PCOS for symptoms suggestive of OSA. While it is probable that PCOS
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22 312 precedes and contributes to the development of OSA, it is also plausible that OSA may
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24 313 contribute to the presentation and worsen the clinical manifestations of PCOS. Both
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26 314 conditions are associated with significant comorbidities in women (*e.g.* depression,
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28 315 unexplained fatigue, hypertension, dyslipidaemia, IR and impaired glucose tolerance), and
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30 316 may progress undiagnosed for prolonged periods. In order to inform clinical practice and
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32 317 support evidence-based guidelines, further clinical research is needed, including prospective
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34 318 cohort studies in obese and non-obese women with PCOS, to study in detail the relationship
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36 319 between these two important and prevalent conditions.
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320 **References**

- 321 1. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and
322 treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin*
323 *Endocrinol Metab.* 2013;98(12):4565-92.
- 324 2. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A,
325 et al. The polycystic ovary syndrome: a position statement from the European Society of
326 Endocrinology. *Eur J Endocrinol.* 2014;171(4):P1-29.
- 327 3. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's
328 health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd
329 PCOS Consensus Workshop Group. *Fertil Steril.* 2012;97(1):28-38 e25.
- 330 4. Kyrou I, Weickert MO, Randeve HS. Diagnosis and Management of Polycystic Ovary
331 Syndrome (PCOS). In: Ajjan R, Orme SM, editors. *Endocrinology and Diabetes* Springer London; 2015.
332 p. 99-113.
- 333 5. Randeve HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, et al. Cardiometabolic aspects
334 of the polycystic ovary syndrome. *Endocr Rev.* 2012;33(5):812-41.
- 335 6. Tahrani AA, Ali A, Stevens MJ. Obstructive sleep apnoea and diabetes: an update. *Curr Opin*
336 *Pulm Med.* 2013;19(6):631-8.
- 337 7. Tahrani AA. Obstructive sleep apnea in patients with diabetes: implications for clinical
338 practice. *Diabetes Management.* 2015;5(6):511-23.
- 339 8. Tahrani AA. Diabetes and sleep apnea. In: DeFronzo RA, Ferrannini E, Alberti G, editors.
340 *International Textbook of Diabetes Mellitus.* 4th ed 2015. p. 316 - 36.
- 341 9. Engleman HM, Douglas NJ. Sleep. 4: Sleepiness, cognitive function, and quality of life in
342 obstructive sleep apnoea/hypopnoea syndrome. *Thorax.* 2004;59(7):618-22.
- 343 10. Greenstone M, Hack M. Obstructive sleep apnoea. *BMJ.* 2014;348:g3745.
- 344 11. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of Obstructive Sleep Apnea: a
345 Population-based Perspective. *Expert Rev Respir Med.* 2008;2(3):349-64.
- 346 12. Altaf QA, Barnett AH, Tahrani AA. Novel therapeutics for type 2 diabetes: insulin resistance.
347 *Diabetes Obes Metab.* 2015;17(4):319-34.
- 348 13. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population
349 health perspective. *Am J Respir Crit Care Med.* 2002;165(9):1217-39.
- 350 14. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of
351 obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin*
352 *Endocrinol Metab.* 2001;86(3):1175-80.
- 353 15. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome
354 is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin*
355 *Endocrinol Metab.* 2001;86(2):517-20.
- 356 16. Gopal M, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of
357 obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. *Sleep Med.*
358 2002;3(5):401-4.
- 359 17. Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin
360 resistance and glucose tolerance in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.*
361 2008;93(10):3878-84.
- 362 18. Yang HP, Kang JH, Su HY, Tzeng CR, Liu WM, Huang SY. Apnea-hypopnea index in nonobese
363 women with polycystic ovary syndrome. *Int J Gynaecol Obstet.* 2009;105(3):226-9.
- 364 19. de Sousa G, Schluter B, Buschatz D, Menke T, Trowitzsch E, Andler W, et al. A comparison of
365 polysomnographic variables between obese adolescents with polycystic ovarian syndrome and
366 healthy, normal-weight and obese adolescents. *Sleep Breath.* 2010;14(1):33-8.
- 367 20. Nandalike K, Agarwal C, Strauss T, Coupey SM, Isasi CR, Sin S, et al. Sleep and
368 cardiometabolic function in obese adolescent girls with polycystic ovary syndrome. *Sleep Med.*
369 2012;13(10):1307-12.

- 1
2
3 370 21. Tock L, Carneiro G, Togeiro SM, Hachul H, Pereira AZ, Tufik S, et al. Obstructive sleep apnea
4 371 predisposes to nonalcoholic Fatty liver disease in patients with polycystic ovary syndrome. *Endocr*
5 372 *Pract.* 2014;20(3):244-51.
- 6 373 22. Chatterjee B, Suri J, Suri JC, Mittal P, Adhikari T. Impact of sleep-disordered breathing on
7 374 metabolic dysfunctions in patients with polycystic ovary syndrome. *Sleep Med.* 2014;15(12):1547-
8 375 53.
- 9 376 23. Barber TM, McCarthy MI, Wass JA, Franks S. Obesity and polycystic ovary syndrome. *Clin*
10 377 *Endocrinol (Oxf).* 2006;65(2):137-45.
- 11 378 24. Horejsi R, Moller R, Rackl S, Giuliani A, Freytag U, Crailsheim K, et al. Android subcutaneous
12 379 adipose tissue topography in lean and obese women suffering from PCOS: comparison with type 2
13 380 diabetic women. *Am J Phys Anthropol.* 2004;124(3):275-81.
- 14 381 25. de Zegher F, Lopez-Bermejo A, Ibanez L. Adipose tissue expandability and the early origins of
15 382 PCOS. *Trends Endocrinol Metab.* 2009;20(9):418-23.
- 16 383 26. Fogel RB, Malhotra A, White DP. Sleep. 2: pathophysiology of obstructive sleep
17 384 apnoea/hypopnoea syndrome. *Thorax.* 2004;59(2):159-63.
- 18 385 27. Huang-Doran I, Franks S. Genetic Rodent Models of Obesity-Associated Ovarian Dysfunction
19 386 and Subfertility: Insights into Polycystic Ovary Syndrome. *Front Endocrinol (Lausanne).* 2016;7:53.
- 20 387 28. Kapsimalis F, Kryger MH. Gender and obstructive sleep apnea syndrome, part 2:
21 388 mechanisms. *Sleep.* 2002;25(5):499-506.
- 22 389 29. Lee EK, Gutcher ST, Douglass AB. Is sleep-disordered breathing associated with miscarriages?
23 390 An emerging hypothesis. *Med Hypotheses.* 2014;82(4):481-5.
- 24 391 30. Baumgartner A, Dietzel M, Saletu B, Wolf R, Campos-Barros A, Graf KJ, et al. Influence of
25 392 partial sleep deprivation on the secretion of thyrotropin, thyroid hormones, growth hormone,
26 393 prolactin, luteinizing hormone, follicle stimulating hormone, and estradiol in healthy young women.
27 394 *Psychiatry Res.* 1993;48(2):153-78.
- 28 395 31. Hall JE, Sullivan JP, Richardson GS. Brief wake episodes modulate sleep-inhibited luteinizing
29 396 hormone secretion in the early follicular phase. *J Clin Endocrinol Metab.* 2005;90(4):2050-5.
- 30 397 32. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance,
31 398 independent of obesity, in polycystic ovary syndrome. *Diabetes.* 1989;38(9):1165-74.
- 32 399 33. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome
33 400 revisited: an update on mechanisms and implications. *Endocr Rev.* 2012;33(6):981-1030.
- 34 401 34. Franks S, Mason H, Willis D. Follicular dynamics in the polycystic ovary syndrome. *Mol Cell*
35 402 *Endocrinol.* 2000;163(1-2):49-52.
- 36 403 35. Pamidi S, Wroblewski K, Broussard J, Day A, Hanlon EC, Abraham V, et al. Obstructive sleep
37 404 apnea in young lean men: impact on insulin sensitivity and secretion. *Diabetes Care.*
38 405 2012;35(11):2384-9.
- 39 406 36. Lindberg E, Theorell-Haglow J, Svensson M, Gislason T, Berne C, Janson C. Sleep apnea and
40 407 glucose metabolism: a long-term follow-up in a community-based sample. *Chest.* 2012;142(4):935-
41 408 42.
- 42 409 37. Yang D, Liu Z, Yang H, Luo Q. Effects of continuous positive airway pressure on glycemic
43 410 control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. *Sleep*
44 411 *Breath.* 2013;17(1):33-8.
- 45 412 38. Iftikhar IH, Khan MF, Das A, Magalang UJ. Meta-analysis: continuous positive airway
46 413 pressure improves insulin resistance in patients with sleep apnea without diabetes. *Ann Am Thorac*
47 414 *Soc.* 2013;10(2):115-20.
- 48 415 39. Yang D, Liu Z, Yang H. The impact of effective continuous positive airway pressure on
49 416 homeostasis model assessment insulin resistance in non-diabetic patients with moderate to severe
50 417 obstructive sleep apnea. *Diabetes Metab Res Rev.* 2012;28(6):499-504.
- 51 418 40. Murri M, Luque-Ramirez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating
52 419 markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-
53 420 analysis. *Hum Reprod Update.* 2013;19(3):268-88.

- 1
2
3 421 41. Zuo T, Zhu M, Xu W. Roles of Oxidative Stress in Polycystic Ovary Syndrome and Cancers.
4 422 Oxid Med Cell Longev. 2016;2016:8589318.
5 423 42. Chattopadhyay R, Ganesh A, Samanta J, Jana SK, Chakravarty BN, Chaudhury K. Effect of
6 424 follicular fluid oxidative stress on meiotic spindle formation in infertile women with polycystic
7 425 ovarian syndrome. Gynecol Obstet Invest. 2010;69(3):197-202.
8 426 43. Lavie L. Oxidative stress--a unifying paradigm in obstructive sleep apnea and comorbidities.
9 427 Prog Cardiovasc Dis. 2009;51(4):303-12.
10 428 44. Sprung VS, Atkinson G, Cuthbertson DJ, Pugh CJ, Aziz N, Green DJ, et al. Endothelial function
11 429 measured using flow-mediated dilation in polycystic ovary syndrome: a meta-analysis of the
12 430 observational studies. Clin Endocrinol (Oxf). 2013;78(3):438-46.
13 431 45. Pertynska-Marczewska M, Diamanti-Kandarakis E, Zhang J, Merhi Z. Advanced glycation end
14 432 products: A link between metabolic and endothelial dysfunction in polycystic ovary syndrome?
15 433 Metabolism. 2015;64(11):1564-73.
16 434 46. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Mughal S, et al. Obstructive sleep apnea
17 435 and diabetic neuropathy: a novel association in patients with type 2 diabetes. Am J Respir Crit Care
18 436 Med. 2012;186(5):434-41.
19 437 47. Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, et al. Vascular
20 438 inflammation in obesity and sleep apnea. Circulation. 2010;121(8):1014-21.
21 439 48. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular signatures of
22 440 obstructive sleep apnea in adults: a review and perspective. Sleep. 2009;32(4):447-70.
23 441 49. Schwarz EI, Puhan MA, Schlatzer C, Stradling JR, Kohler M. Effect of CPAP therapy on
24 442 endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis.
25 443 Respirology. 2015;20(6):889-95.
26 444 50. Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activation in visceral obesity.
27 445 Circulation. 2002;106(20):2533-6.
28 446 51. Bell BB, Rahmouni K. Leptin as a Mediator of Obesity-Induced Hypertension. Curr Obes Rep.
29 447 2016;5(4):397-404.
30 448 52. Lansdown A, Rees DA. The sympathetic nervous system in polycystic ovary syndrome: a
31 449 novel therapeutic target? Clin Endocrinol (Oxf). 2012;77(6):791-801.
32 450 53. Sverrisdottir YB, Mogren T, Kataoka J, Janson PO, Stener-Victorin E. Is polycystic ovary
33 451 syndrome associated with high sympathetic nerve activity and size at birth? Am J Physiol Endocrinol
34 452 Metab. 2008;294(3):E576-81.
35 453 54. Grassi G, Facchini A, Trevano FQ, Dell'Oro R, Arenare F, Tana F, et al. Obstructive sleep
36 454 apnea-dependent and -independent adrenergic activation in obesity. Hypertension. 2005;46(2):321-
37 455 5.
38 456 55. Xie A, Skatrud JB, Puleo DS, Morgan BJ. Exposure to hypoxia produces long-lasting
39 457 sympathetic activation in humans. J Appl Physiol (1985). 2001;91(4):1555-62.
40 458 56. Loreda JS, Ziegler MG, Ancoli-Israel S, Clausen JL, Dimsdale JE. Relationship of arousals from
41 459 sleep to sympathetic nervous system activity and BP in obstructive sleep apnea. Chest.
42 460 1999;116(3):655-9.
43 461 57. Hedner J, Darpo B, Ejjnell H, Carlson J, Caidahl K. Reduction in sympathetic activity after long-
44 462 term CPAP treatment in sleep apnoea: cardiovascular implications. Eur Respir J. 1995;8(2):222-9.
45 463 58. Tasali E, Chapotot F, Leproult R, Whitmore H, Ehrmann DA. Treatment of obstructive sleep
46 464 apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. J
47 465 Clin Endocrinol Metab. 2011;96(2):365-74.
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Study	Notes	n	OSA		Women with PCOS and OSA compared to women with PCOS without OSA							
			Diagnosis	%	Weight or BMI	WC or WHR	IR	Hyperandrogenism	BP	FPG	IGT	MS
Vgontzas et al. 2001; (15)	USA	53	AHI ≥ 10 + symptoms	11–17%	↑	NA	Insulin ↑*	FT and TT ↔	NA	↔	NA	NA
Fogel et al. 2001; (14)	USA	18	AHI >10	66.8%	NA	↑	NA	NA	NA	NA	NA	NA
Gopal et al. 2002; (16)	USA	23	RDI ≥ 5 + symptoms	69.6%	↔	NA	NA	NA	NA	NA	NA	NA
Tasali et al. 2008; (17)	USA	52	AHI ≥ 5	55.8%	↑	NA	HOMA-IR ↑*	FT and TT ↔	NA	↔	↑	NA
Yang et al. 2009; (18)	Taiwan, lean women	18	AHI ≥ 5	0%								
De Sousa et al. 2010; (19)	Germany, adolescents	22	Not stated	0%								
Nandalike et al. 2012; (20)	USA, adolescents, retrospective	28	AHI >5 or apnoea index >1	57.2%	↔	NA	HOMA-IR ↑	FT and TT ↔	↑	↔	NA	↑
Tock et al. 2014; (21)	Brazil	38	AHI ≥ 5	31.6%	↑	↑	HOMA-IR ↑	FT ↑*	NA	↔	↑	NA
Chatterjee et al. 2014; (22)	India	50	RDI ≥ 5 + symptoms or RDI >15	66%	↑	↑	HOMA-IR ↔	FT ↔	↑	↑*	NA	↑

Table 1 Differences between women with PCOS and OSA compared to women with PCOS only. n, number of participants; OSA, obstructive sleep apnoea; PCOS, polycystic ovary syndrome; AHI, apnoea/hypopnea index; RDI, respiratory distress index; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip-ratio; IR, insulin resistance; HOMA-IR, homeostatic model assessment of insulin resistance; FT, Free testosterone; TT, total testosterone; BP, blood pressure; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; MS, metabolic syndrome; ↑ statistically significant increase; NA, not available; ↔ equal; *adjusted for weight.

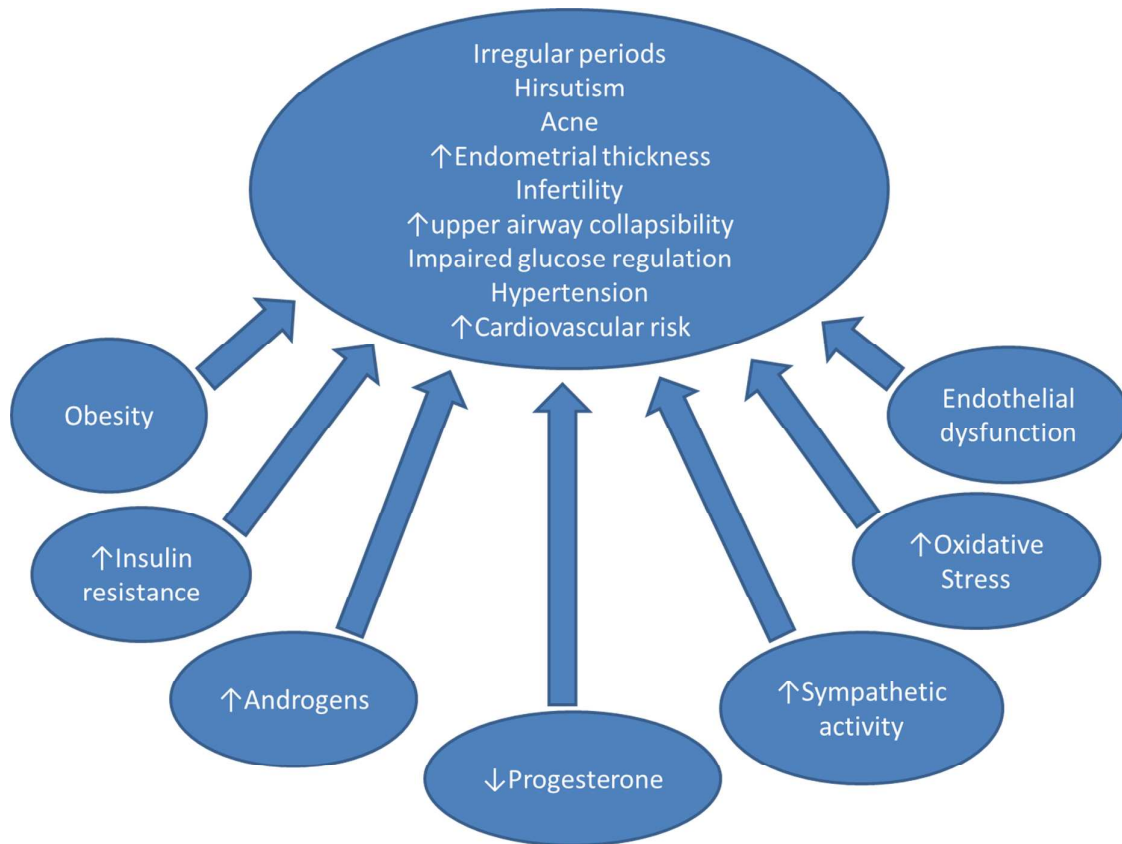


Figure 1. Possible mechanisms linking common shared features between Obstructive Sleep Apnoea (OSA) and Polycystic Ovary Syndrome (PCOS) with their clinical consequences.