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

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

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Abstract

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

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 co-morbidities, 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,

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

Despite the high prevalence of OSA in the general population, this condition is generally under-recognised and frequently remains undiagnosed in everyday clinical practice, particularly in women who may not present with typical OSA symptoms (11). As obesity is a common risk factor, it is not surprising that OSA and PCOS might co-exist. The association between PCOS and OSA has also been recognised in the latest guidelines by the European and the US Endocrine Societies (Box 1) (1, 2). However, these guidelines acknowledge the limited evidence behind their recommendations that is largely based on limited, 'weak', or 'low quality' data. This highlights the need for further research to better understand the relationship between PCOS and OSA. In addition, the implications of OSA in women with PCOS are not clear, though important as both conditions are associated with overlapping comorbidities, and OSA is associated with essential factors that may contribute to the burden of PCOS (*e.g.* to IR, increased inflammation, and oxidative stress) (6, 12). In this article we present a concise review of key studies that examined the relationship between OSA and PCOS, and we explore the potential mechanisms linking both conditions.

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

1. Endocrine Society, 2013 (1):
We suggest screening overweight/obese adolescents and women with PCOS for symptoms suggestive of OSA and, when identified, obtaining a definitive diagnosis using polysomnography. If OSA is diagnosed, patients should be referred for institution of appropriate treatment.

2. European Society of Endocrinology, 2014 (2):
It seems wise at this moment to screen sleep disorders by clinical questionnaires in obese women with PCOS. In the case of clinical suspicion resulting from these questionnaires, patients should be referred to a centre of sleep disorders for polysomnography and further evaluation.

2. Methodology

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

3. Epidemiology

3.1 PCOS prevalence in OSA

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

3.2 OSA prevalence in PCOS

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

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

ranges from 0% to 69% (median: 55.8%; mean: 39.8%). This large variability and wide range in the reported prevalence may be attributed to a combination of reasons, including application of different cut-off points and methods to diagnose OSA, the small size of the studied cohorts, and potential selection bias by recruitment of study participants from specialised clinics. As expected, the available data suggest that OSA risk in women with PCOS is increased with age and obesity. While the only published study that examined the presence OSA in lean women with PCOS showed no evidence of the condition (18), the small number of study participants (n=18) precludes generalisability or drawing firm conclusions from these data. The reported prevalence and potential links between PCOS and OSA in adolescents are even more controversial, with one study showing a prevalence of 16/28 (57%) (20) and another showing 0/22 (0%) prevalence (19). Based on the available data on the prevalence and natural history of these two conditions, it is probable that PCOS precedes the development of OSA; however, it cannot be excluded that OSA may precede the clinical presentation of PCOS in some women, worsening the PCOS-related symptomatology. Observational long-term studies are needed to accurately assess the incidence of OSA in women with PCOS and *vice versa*.

4. Proposed mechanisms linking OSA to PCOS and its comorbidities

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

smaller upper airway; altering the neural compensatory mechanisms that maintain airway patency; reducing the functional residual capacity with a resultant decrease in the stabilising caudal traction on the upper airway; reducing lung volume due to increased abdominal fat; increasing breathing workload due to increased chest wall thickness; and affecting the chemosensitivity to O_2 and CO_2 which reduces the ventilatory drive (8, 26). Subsequently, obesity is a key factor that predisposes to both PCOS and OSA. However, other shared features between PCOS and OSA may also play an important mechanistic role in the development/interaction between these two common conditions.

4.1 Sex Hormones

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

4.2 Insulin resistance

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

4.3 Oxidative stress

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

(43). Subsequently, OSA may complicate the clinical picture in PCOS by promoting oxidative stress.

4.4 Endothelial dysfunction

Women with PCOS have been found to have lower flow-mediated dilatation (FMD) compared to age- and weight-matched controls (44). Obesity, IR, oxidative stress, advanced glycation end products (AGE) and inflammation are believed to play a role in the pathogenesis of endothelial dysfunction in PCOS (45). OSA is also associated with endothelial dysfunction and the underlying mechanisms are likely related to ischemia-reperfusion injury (46). Repetitive episodes of re-oxygenation after hypoxemia in patients with OSA result in increased production of AGE and ROS (43); altered protein kinase C signaling; decreased endothelial nitric oxide synthase (47); increased endothelin-1 levels and inflammation (48). Notably, CPAP treatment was found to increase FMD in patients with OSA (49).

4.5 Sympathetic activity

Sympathetic activity is increased in obesity and is associated with visceral adiposity (50); high leptin levels (51) and IR (52) are thought to play a role in its pathogenesis. However, increased sympathetic activity may further exacerbate IR and creates a vicious cycle (52). Women with PCOS have evidence of increased sympathetic activity (52), even in the absence of obesity (53). Sympathetic activity may contribute to the pathogenesis of PCOS through increased IR, altered ovarian function and the development PCO morphology (52). OSA is also associated with an increase in sympathetic activity independent of body weight (54). It is likely that both the recurrent hypoxia (55) and recurrent arousals (56) contribute to the activation of the sympathetic nervous system (SNS). Moreover, treatment with CPAP is associated with a reduction in sympathetic activity (57).

4.6 Summary of the proposed mechanisms linking OSA and PCOS

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

5. The impact of OSA in women with PCOS

5.1 Review of published studies

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

In the study by Vgontzas *et al.* (15), women with PCOS and sleep disordered breathing (SDB was defined as either OSA or upper airway resistance syndrome; n=9) were heavier (BMI 45.7±2.6 *vs.* 37.2±1.1 kg/m^2, P<0.003), and had higher fasting insulin (306.5±52.4 *vs.* 176.1±18.5 pmol/L, P<0.01) and lower glucose-to-insulin ratio (0.02±0.006 *vs.* 0.04±0.003, P<0.05) compared to women with PCOS without SDB (n=44). Logistic regression analysis of the study data showed that insulin levels and glucose-to-insulin ratio had a stronger association with SDB than age, BMI, or testosterone levels. However, the difference in BMI between the two groups in this study was rather high (8.5 kg/m^2), and despite statistical

adjustment, it is difficult to completely rule out an effect of obesity on the metabolic differences between the two groups.

Similarly, in the study by Tasali *et al.* (17), women with PCOS and OSA (n=29) were older (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/m^2 ; P<0.001), and were more insulin resistant (HOMA-IR 5.7±0.4 *vs.* 3.5±0.4, P=0.006) than women with PCOS without OSA (n=23). After controlling for age, BMI, and ethnicity, AHI was a highly significant predictor of the fasting concentrations of glucose and insulin, as well as of the 2-h glucose concentration (after an oral glucose tolerance test) and HOMA-IR. The data of this study also suggest that the degree of sleep fragmentation, rather than the severity of hypoxia, may be related to the severity of IR and glucose intolerance in women with PCOS. As such, the authors further concluded that women with PCOS and OSA represent a metabolically different, 'higher risk' population compared to women with PCOS without OSA. However, this conclusion should be taken with caution considering the small study sample size, and the relatively large difference in BMI (7.1 kg/m^2) between women with and without OSA in this study.

Notably, Tasali *et al.* have also conducted a relevant short-term interventional study (58) in 19 obese women with PCOS and OSA (age ± SEM: 31.2±1.2 years; BMI: 46.4±2.4 kg/m^2). These women were treated with CPAP for 8 weeks, exhibiting subsequent improvement in insulin sensitivity (relative increase of nearly 7%), and reduction in diastolic blood pressure (DBP; approximately 2.3 mmHg). In addition, day-time and night-time norepinephrine levels also reduced after CPAP therapy. However, this study lacked a control group, and only a 'per protocol' analysis was performed including just 9 study participants, with the data from another 10 study patients being excluded from the analysis due to lack of adequate CPAP treatment compliance (average use of CPAP <4 hours per night). Of note, whether the

reported post-treatment changes in IR and blood pressure observed in this study may translate/result into meaningful clinical outcomes remains to be studied.

In another study by Tock *et al.* (21), women with PCOS and OSA (n=12) had higher BMI (37.8±4.8 *vs.* 30.67±7.7 kg/m^2, P=0.006); waist circumference (114.4±12.0 *vs.* 98.1±19.9 cm, 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.* 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 (205.0±28.7 *vs.* 172.3±35.8 mg/dL, P=0.009); low density lipoprotein-cholesterol (LDL, 128.6±21.6 *vs.* 98.9±29.6, P=0.004); and higher prevalence of non-alcoholic fatty liver disease (NAFLD, 83.3% *vs.* 26.9%, P<0.001) compared to those without OSA (n=26). After adjusting for obesity in multivariate logistic regression analysis, raised serum free testosterone levels ≥1.07 ng/dL increased the risk of OSA in women with PCOS by 8.2 fold. Accordingly, the authors concluded that hyperandrogenism may be a predisposing factor for OSA in PCOS. However, a limitation of this study is the fact that testosterone was measured by immunoassay rather than by tandem mass spectrometry. In a subsequent multiple logistic regression analysis, with OSA (AHI ≥5), IR (HOMA-IR ≥2.7), and obesity (BMI ≥30 kg/m^2) considered as independent variables and NAFLD as the dependent variable, only OSA was an independent predictor of the presence of NAFLD. The presence of OSA increased the chance of NAFLD 7.6 fold in woman with PCOS. As such, the authors concluded that OSA is a predictor of NAFLD along with, but independent of, obesity and IR.

In a recent study by Chatterjee *et al.* (22), women with PCOS and SDB (n=33) had higher BMI (29.8±3.4 *vs.* 24.36±2.29 kg/m^2, P<0.001), waist circumference (95.58±6.47 *vs.* 85.12±4.34, P<0.001), systolic BP (SBP, 129.27±10.93 *vs.* 119.18±8.03 mmHg, P=0.002), diastolic BP (78.61±9.07 *vs.* 73.53±6.22 mmHg, P=0.044), and hirsutism (Ferriman–Gallwey score 9.82±2.78 *vs.* 8.00±2.5, P=0.028) compared to women with PCOS without SDB

(n=17). Interestingly, in a logistic regression analysis which adjusted for BMI, only the associations between fasting plasma glucose and diastolic BP with SDB remained significant.

Finally, in the study by Nandalike *et al.* (20), adolescent girls with PCOS and OSA (n=16) had higher prevalence of the metabolic syndrome (56.3% *vs.* 8.3%, P=0.03); higher HOMA-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), triglycerides (149.7±87.7 *vs.* 93.3±25.8 mg/dl, P=0.03), and lower high density lipoprotein (HDL, 38.6±8.7 *vs.* 49±10.9 mg/dl, P=0.01) compared to girls with PCOS without OSA (n=12).

5.2 Summary of the literature

It seems plausible that OSA is associated with the severity of the PCOS phenotype, particularly in overweight/obese and insulin resistant women with PCOS. However, it is difficult to draw firm conclusions from the studies conducted so far since significant variables (*e.g.* abdominal adiposity and ethnicity) have often not been accounted for in the presented analyses. In addition, while the association between OSA and increased insulin resistance in women with PCOS seems to be a common theme, the relationship between OSA and hyperandrogenism is more controversial and require further evaluation. While the US and European Endocrine societies' guidelines consider the presence of OSA as a cardiovascular risk factor in women with PCOS (1, 2), there is lack of data on the exact relationship between OSA and important clinical outcomes in women with PCOS (*e.g.* on T2DM risk, cardiovascular risk, subfertility, depression, and impaired QoL). Subsequently, well conducted observational studies are needed to examine the effects of OSA in women with PCOS. Interventional studies are also required in women with PCOS and OSA. The existing short-term, pilot, interventional study in such patients suggests that CPAP therapy

may significantly improve insulin sensitivity and reduce blood pressure. However, it remains unclear whether this can translate into long-term meaningful clinical outcomes.

6. Conclusions

OSA appears to be common in obese women with PCOS. There is a lack of high-quality evidence regarding the clinical benefit or the cost-effectiveness of the current Endocrine Society clinical practice guidelines which suggest screening all overweight/obese adolescents and women with PCOS for symptoms suggestive of OSA. While it is probable that PCOS precedes and contributes to the development of OSA, it is also plausible that OSA may contribute to the presentation and worsen the clinical manifestations of PCOS. Both conditions are associated with significant comorbidities in women (*e.g.* depression, unexplained fatigue, hypertension, dyslipidaemia, IR and impaired glucose tolerance), and may progress undiagnosed for prolonged periods. In order to inform clinical practice and support evidence-based guidelines, further clinical research is needed, including prospective cohort studies in obese and non-obese women with PCOS, to study in detail the relationship between these two important and prevalent conditions.

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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	Hyperandro-genism	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.

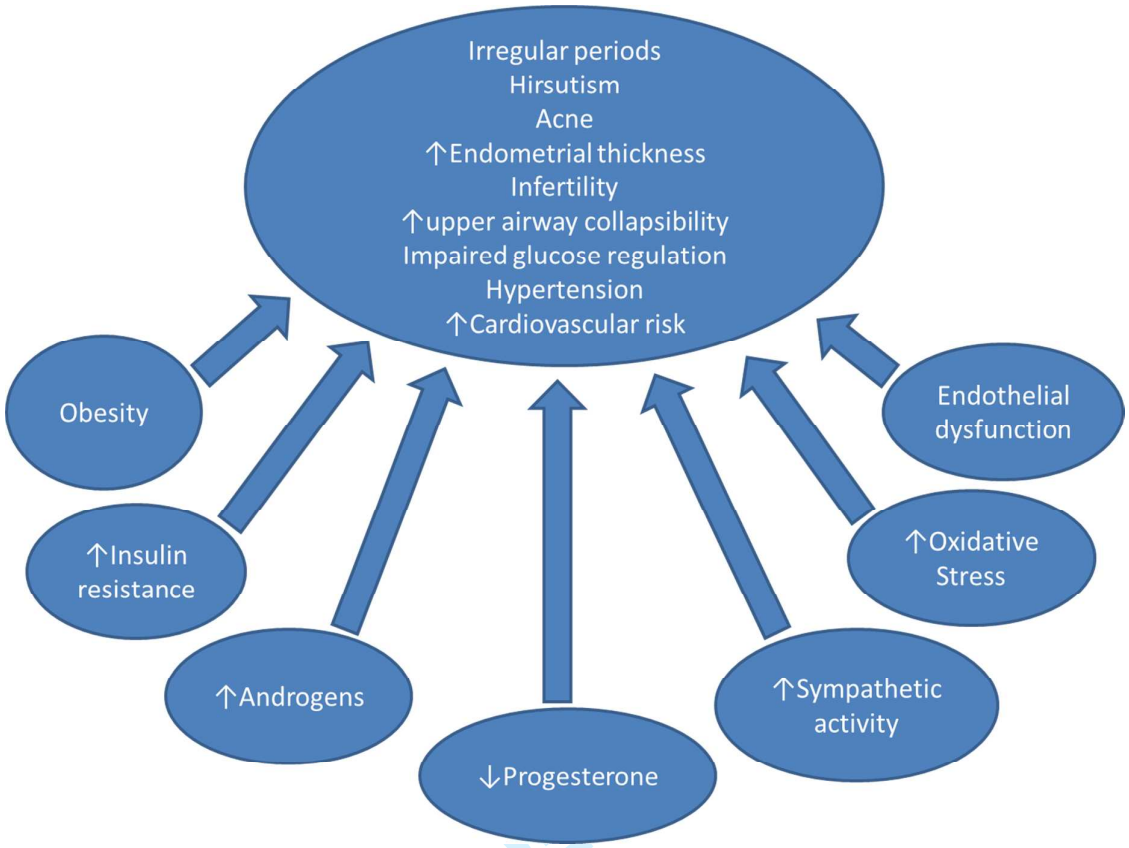

Figure 1. Possible mechanisms linking common shared features between Obstructive Sleep Apnoea (OSA) and Polycystic Ovary Syndrome (PCOS) with their clinical consequences.