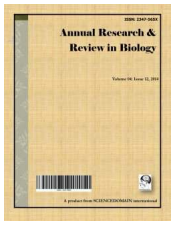

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Psychoneuroendocrinology Aspect of Sleep Pattern in Women with Polycystic Ovary Syndrome

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common complex condition in women associated with reproductive, metabolic and psychological features. PCOS is the most common endocrine disorder in the reproductive age of women. These patients are prone to develop sleep-disordered breathing (SDB), metabolic disorders and cardiovascular disease (CVD). Studies over the past decade show that lifestyle can help in disease progression. Various lifestyle factors play an important role as prevalence of PCOS is rising in adolescents, particularly with the endorsement of modernized lifestyle. Sleep is an important part of health and wellness. Recent studies have showed that, a reduced sleep duration and quality sleep can have an effect on hypothalamus-pituitary-adrenal (HPA) axis activity. The HPA axis is under regulatory control of circadian oscillators and reduced sleep duration and quality sleep can have an effect on HPA axis activity. In this study we review the quality of sleep and stress in women with PCOS.

Keywords: Polycystic ovary syndrome (PCOS); sleep; HPA; stress; lifestyle.

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ABBREVIATIONS

PCOS : Polycystic ovary syndrome
SDB : Sleep-disordered breathing
CVD : Cardiovascular disease
HPA : Hypothalamus-pituitary-adrenal
REM : Rapid eye movement
Non-REM : Slow waves
ACTH : Adrenocorticotropic hormone
CRH : Corticotrophin-releasing hormone
CAR : Cortisol awakness response
LC : Locus coeruleus
NA : Noradrenergic
VLPO : Ventrolateral preoptic area
DRN : Dorsal raphe nuclei
HPO : Hypothalamic-pituitary-ovarian
GnRH : Gonadotropin-releasing hormone
POMC : Proopiomelanocortin
HRQL : Health-related quality of life
GR : Glucocorticoid receptor
ART : Assisted reproductive technology

1. INTRODUCTION

1.1 Sleep

Human spent almost a third of their lives asleep, but still the function of this behavior is not well understood. Sleep is an important part of health and wellness, because it is an important component of human homeostasis. Sleep disorders are closely associated with significant medical, psychological and social disturbances. Chronic sleep restriction is an increasing problem in many countries. Since the body's stress systems play a critical role in adapting to a continuously changing and challenging environment, it is an important question whether these systems are affected by sleep loss. The human body mobilizes defensive processes in an adaptive effort to maintain homeostasis. If these defenses fail, insomnia may occur. Short-term insomnia is caused by a change in routine such as psychiatric illness, disability, and stress [1]. Sleep is a psycho- neurophysiologic process that its history is from eighteenth century. The electrical activity of sleep is recorded from sixty years ago. This activity includes two sleep phases: rapid eye movement (REM) and slow waves (Non-REM). Recent studies have showed that, a reduced sleep duration and quality sleep can have an effect on hypothalamus-pituitary-adrenal (HPA) axis activity. Last studies show that the early morning rise of ACTH and cortisol is reduced when additional energy is provided. This finding supports the view that the nocturnal rise in HPA axis activity contributes to preparing the organism for the upcoming wake period and associated increased energy demands [2,3,4,5].

1.2 Sleep & HPA

The hypothalamus-pituitary-adrenal (HPA) axis is under regulatory control of circadian oscillators, yielding a distinct 24-h rhythm of cortisol secretion from the adrenal cortex [6,7]. In the beginning of sleep, the activity of HPA axis is suppressed continually. In the latter part of sleep, the HPA secretory activity increases so it is close to the maximum circadian rhythm immediately after waking up, and the prominent activity of the HPA axis and sympathetic nervous system influences the overall amount of rapid eye movement (REM) sleep [8]. Therefore, the rise of adrenocorticotrophic hormone (ACTH) in the morning is the decisive control factor regulating the end of sleep [9]. Activation of the HPA and/or the sympathetic nervous systems results in wakefulness and these hormones including corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol or corticosterone, noradrenaline, and adrenaline, are associated with attention and arousal. Stress-related insomnia leads to a vicious circle by activating the HPA system. An awareness of the close interaction between sleep and stress systems is emerging and the hypothalamus is now recognized as a key center for sleep regulation, with hypothalamic neurotransmitter systems providing the framework for therapeutic advances. The fact that the beginning and end of sleep involve HPA axis activity and the close temporal relationship between the axis and sleep provides a clue to estimate the effects of the stress on sleep [10]. On the other hand, since the HPA axis is a vital part of the human stress response system, cortisol responses to psychological or physiological stress exposure can superimpose the circadian rhythm. Cortisol has ubiquitous effects in the body and affects cognitive as well as emotional networks of the central nervous system [11,12,13]. After awakening lower cortisol levels immediately were found to be related to poor sleep quality in patients with primary insomnia [14]. Notably, the cortisol awakeness response (CAR) has been found to be abolished in patients with memory disorders due to damage in the frontal lobes or the hippocampal region [15,16]. The fact that cortisol concentrations increase already several hours before awakening strongly supports the notion that the CAR amplitude is partially determined also by circadian factors. This view is corroborated by Wilhelm et al. [17] finding that

peak cortisol levels of the CAR were not independent from (but negatively correlated with) the average cortisol concentrations during the night. One possible candidate that likely contributes to the awakening response is the adrenergic locus coeruleus (LC) which is strongly activated at the transition to wakefulness [17]. Noradrenergic (NA) neurons of the LC spread out widely to the overall brain, and they activate alertness, followed by NREM, with activity being lowest during REM sleep [18]. When the LC is stimulated, the activity of the cerebral cortex (i.e., EEG) is increased [19] and the changes in the LC activity are increased by new stimulation and various stressors. Stress may activate the LC activity by secretion of corticosteroid releasing hormone (CRH) in the paraventricular nucleus of the hypothalamus [20]. However, HPA axis plays important roles in maintaining alertness and modulating sleep. Sleep and alertness are mutually competitive and necessarily exclusive; the development of alertness is the reverse of sleep pressure. LC/NA is a center for alertness and Preoptic area (POA) is a center of sleep.

1.3 Sleep & Preoptic Area (POA)

The ventrolateral preoptic area (VLPO) as a sleep center contains GABAergic/galaninergic neurons, which act as an inhibitory neuro-transmitter. POA neurons principally use histamine, and so assume to be involved in alertness and NREM [21,22]. VLPO neurons send terminals to the dorsal raphe nuclei (DRN) and LC, which have important roles for REM. Conversely, GABAergic neurons in the VLPO are suppressed by noradrenalin and serotonin [23]. The interaction between the VLPO and the branches of the ascending arousal pathway is mutually inhibiting, functioning much like an electrical “on-off” switch, enabling the body to maintain a stable state of wakefulness and sleep [24,25]. Normally, this “sleep-wake switch” design ensures stability between sleep and wakefulness while promoting rapid transitioning between the two behavioral states. Sleep disorders represent pathology of this switch, which causes individuals to suffer from state instability, with wake intruding into sleep and/or sleep intruding into wake [26].

1.4 Sleep Disorders

The estimated prevalence of syndromes of sleep-wake disorders in the US is about 50 to 70 million [27] and those who suffer from chronic sleep disorders have impaired daily functioning, compromised health status, and diminished quality of life [28]. It is now apparent that the neural circuitry underlying the regulation of sleep and wakefulness is discrete for each state yet interdependent; the very arousal systems that are inhibited by sleep-promoting neurons also serve to disrupt these same sleep processes to return the body to a wakeful state [29].

1.5 Sleep & Stress

Stress activates two Axes: HPA and the sympatho-adreno-medullary (SAM) systems, influencing cardiovascular, catecholamine, cortisol, ACTH, and CRH hyperactivity [30]. Increased activity of the autonomic nervous system [31] and cortisol causes alertness. Increased ACT influences awakening. Therefore, awakening from sleep after stress can be related to the early increase of ACTH [32]. It has been shown that the injection of ACTH increases sleep latency, decreases slow wave sleep, and fragments sleep [33]. CRH acting as a neurotransmitter in the LC activates noradrenaline neurons in the LC. But, under chronic stress, distal corticosteroids increase and sleep is disrupted [10]. Insomnia causes physiological responses like those in stress situations. Sleep increases growth hormone and testosterone [34] and reduces metabolism and blood flow, to fight against stress [35]. In a state of insomnia, cortisol, heart rate, central temperature, and oxygen consumption are increased [8] as are glucose tolerance [36] and cytokines [37]. Evidence to date indicates (bit has not confirmed) a close connection between stress and sleep. Stress causes psycho-physiological responses and activates the HPA system, which are incompatible with normal sleep. Also, insomnia causes a vicious circle of stress-insomnia by further activating the HPA system. Especially, chronic stress can cause continuous hippocampus-related memory system fatigue by up-regulating the HPA system. The long-term impacts of chronic stress remain unclear [10].

2. POLYCYSTIC OVARY SYNDROME (PCOS)

PCOS is a complex, multifaceted, heterogeneous disorder, affecting 4% to 18% of reproductive-aged women and is associated with reproductive, metabolic and psychological dysfunction [38]. A 2004 consensus conference added another diagnostic criterion, multicystic ovarian morphology (ultrasonographic) and required two of the three criteria to support the diagnosis [39].

The precise etiology of the disease is so far still unknown, but there are indications that PCOS is associated with hyperactivity in the sympathetic nervous system [40]. Evidence from studies on women with PCO and on an experimental rat PCO model suggests that the sympathetic regulatory drive to the ovary may be unbalanced. Most reports support the theory that increased sympathetic activity contributes to the development and maintenance of PCOS. The results of our study in 2011 showed that antagonized the hyperactivity of the sympathetic nervous system results in the treatment of PCO modeling in rat [41]. Thus, there is a possibility that increased ovarian NE concentrations represent changes in the activity of sympathetic nerves, which consequently participate in the process of ovarian cyst formation observed during ageing in the human and experimental animal models [42].

2.1 PCOS & HPA

The female reproductive system is regulated by two axes: The HPA and hypothalamic-pituitary-ovarian (HPO) axes, that the principal regulators of these axes are CRH and GnRH that stimulates FSH and LH secretion and, subsequently, estradiol and progesterone secretion by the ovary [43]. Hypothalamic target neurons of estrogen include neurosecretory neurons such as gonadotropin-releasing hormone (GnRH) and dopamine neurons, and local circuitry neurons such as proopiomelanocortin (POMC). These and other hypothalamic neurons are involved in regulating numerous homeostatic functions including reproduction, thermoregulation, stress responses, feeding and motivated behaviors [44]. The HPA axis, when activated by stress, exerts an inhibitory effect on the female reproductive system, corticotrophin releasing hormone and CRH-induced proopiomelanocortin peptides, such as β-endorphin, inhibit hypothalamic GnRH secretion [45]. In addition, glucocorticoids suppress gonadal axis function at the hypothalamic, pituitary and uterine level [46]. Glucocorticoid administration significantly reduces the peak luteinizing hormone response to intravenous GnRH, suggesting an inhibitory effect of glucocorticoids on the pituitary gonadotrophins [47].

2.2 PCOS & Stress

Studies in recent decades have shown that lifestyle intervention improves body composition and so modifying sleep patterns in these patients may be able to regulate the hormonal balance in the brain-ovary axis. In this review we investigate the sleep factor of lifestyle in these patients. Roos et al. in [48] reported determining the relationship between insulin resistance and psychiatric distress in PCOS. Adali´s and Hirschberg´s results [49,50] suggesting that the therapy of PCOS should tackle both physical and psychological complaints. This is because psychological distress reduces motivation, and yet good motivation is the key to agreement with medication and dietary management of PCOS [51,52]. Also these data confirm Barry et al. [53] on seventy-six women with PCOS and 49 subfertility controls that reported their anxiety, depression and aggression levels. They reported that women with PCOS were significantly more neurotic (had difficulty coping with stress) than controls, had more anxious and depressed than controls. The study on PCOS patients in South Asians shows adversely affects their psychological wellbeing and health-related quality of life. Their psychological distress is related to hirsutism rather than to obesity [54]. Indian studies on psychological stress by Goldberg's GHQ 28 (General Health Questionnaire) assessed psychological status, in ninety nine women with PCOS. This psychological study has showed that 72% had obesity, 70% had hirsutism and 72% had a waist circumference >88 cm. All these variables were statistically significant and Indian women presenting with PCOS had increased psychological distress [55]. Our study show [56,57,58] that clinical signs of PCOS are the most closely associated with psychological distress and this data was undertaken in order to clarify the relationship between increased emotional stress, anxiety symptoms, and the clinical characteristics of PCOS in a group of young patients with PCOS.

2.3 PCOS & Sleep

Few studies have been done on the sleep duration and health-related quality of life (HRQL). Women with PCOS are known to have poorer sleep. The study of Shreeve et al. [59] in 2013 showed that PCOS women had significantly elevated night-time urinary levels of the melatonin metabolite 6-sulfatoxymelatonin (aMT6s) and of 8-OHdG, as well as significantly reduced sleep quality, compared with the controls. Our results in 2014 showed that serum levels of melatonin and β-endorphin were lower in women with PCOS and serum level of stress hormones; adrenaline and noradrenaline were significantly correlated with patients' sleep time in

study group. Also our study showed that the levels of adrenaline and noradrenaline in PCO women with early sleep are much lower than patients who slept later at night. Only cortisol has significant relation with PSQI global score by regression analysis and it associated with time of sleep. Although cortisol level in control group on women with more than 8 hours sleep is significantly lower than women without 8 hours sleep. This data showed that a good night's sleep can reduce stress hormones [60]. Milutinovic's hypothesize in 2011 is that modulation of glucocorticoid receptor (GR) expression and function may underlie possible PCOS-related impairment of feedback inhibition of HPA axis activity and imply that PCOS is associated with increased GR protein concentration and HPA axis sensitivity to dexamethasone [61]. Then up-regulation of GR can be the reason of normal rate of cortisol in women with PCO.

2.4 PCOS & Lifestyle

Overweight and obesity are present in 30% to 70% of women with PCOS and worsen the PCOS symptom profile. More specifically, the prevalence's of hirsutism, menstrual cycle irregularities, anovulation, and infertility are greater in overweight and obese women with PCOS than in women of normal weight with PCOS [62,63]. Overweight in women with PCOS also has a negative influence on women's health-related quality of life (HRQoL) [64]. Then the crucial first step of treatment of PCO women is weight loss in overweight women. Evidence about the isolated effect of exercise and diet interventions on psychological well-being in women with PCOS is limited [65]. Liao et al. [66] in 2008 found that a self-directed walking program significantly reduced the level of body image distress in overweight women with PCOS. Galletly et al. [67] in 2007 reported a lower depression rate and higher level of self-esteem after a high-protein diet when compared with a low-protein diet. To date, there is no evidence about the isolated effect of psychological interventions on the psychological well-being of women with PCOS [65]. The relationship between polycystic ovary syndrome and sleep condition such as insomnia and sleep apnea is very complex and has not been done much research in this area.

3. CONCLUSION

The aim of this review was the investigation the link of PCOS and sleep/stress. Stress can disturb the enough sleep and can stop us going to sleep. Stress can alter normal sleep pattern. Unbalanced hormone levels in PCOS causes metabolic syndrome, mood swings (irritability, depression and anxiety), sleep problem and eventually infertility in this women. Quality lifestyle can have a positive role in the outcome of infertility and assisted reproductive technology (ART) in women with PCOS. The physiological homeostasis in the body makes healthy lifestyle. When physiological homeostasis established stress management is possible. Management of stress can normalize the activity of the brain-ovary axis. The health of the female reproductive system is defined by the dominant follicle that lifestyle (stress, food, sleep and exercise) plays an important role in this cycle.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Partinen M. Sleep disorders and stress. J Psychosom Res. 1994;38(Suppl 1):89–91.
2. Born J, Hansen K, Marshall L, Molle M, Fehm HL. Timing the end of nocturnal sleep. Nature. 1999;397:29-30.
3. Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: Clinical implications. J Clin Endocrinol Metab. 2001;86:3787-94.
4. Balbo M, Leproult R, Cauter E. Impact of sleep and its disturbances on Hypothalamo-pituitary-adrenal axis activity. International Journal of Endocrinology. 2010;2010:16. (Article ID 759234)
5. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. Sleep Sci. 2015;8: 143-152.
6. Hellman L, Nakada F, Curti J, Weitzman ED, Kream J, Roffwarg H, Ellman S, Fukushima DK, Gallagher TF. Cortisol is secreted episodically by normal man. J. Clin. Endocrinol. Metab. 1970;30:411–422.
7. Gallagher TG, Yoshida K., Roffwarg HD, Fukushima DK, Weitzman ED, Hellman L. ACTH and cortisol secretory patterns in man. J. Clin. Endocrinol. Metab.1973;36: 1058–1068.

8. Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: Clinical implications. J Clin Endocrinol Metab. 2001;86:3787–3794.
9. Weibel L, Follenius M, Spiegel K, Ehrhart J, Brandenberger G. Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. Sleep. 1995;18: 549–556.
10. Han KS, Kim L, Shim I. Stress and sleep disorder. Exp Neurobiol. 2012;21(4): 141–150.
11. Belanoff JK, Gross K, Yager A, Schatzberg AF. Corticosteroids and cognition. J Psychiatr Res. 2001;35:127–145.
12. McEwen BS. Interacting mediators of allostasis and allostatic load: Towards an understanding of resilience in aging. Metabolism. 2003;52:10-16.
13. Het S, Ramlow G, Wolf OT. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology. 2005;30: 771–784.
14. Backhaus J, Junghanns K, Hohagen F. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. Psychoneuroendocrin. 2004;29: 1184–1191.
15. Buchanan TW, Kern S, Allen JS, Tranel D, Kirschbaum C. Circadian regulation of cortisol after hippocampal damage in humans. Biol. Psychiatry. 2004;56: 651–656.
16. Wolf OT, Fujiwara E, Luwinski G, Kirschbaum C, Markowitsch HJ. No morning cortisol response in patients with severe global amnesia. Psychoneuroendocrinology. 2005;30:101–105.
17. Wilhelm I, Born J, Kudielka MB, Schlotz W, Wüst S. Is the cortisol awakening rise a response to awakening? Psychoneuroendocrinology. 2007;32: 358-366.
18. Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: Neuronal systems, consciousness and learning, Nat. Rev. Neurosci. 2002;3:679-693.
19. Chu N, Bloom FE. Norepinephrine-containing neurons: Changes in spontaneous discharge patterns during sleeping and waking. Science. 1973;179: 908–910.
20. Berridge CW, Foote SL. Effects of locus coeruleus activation on electroencephalographic activity in neocortex and hippocampus. J Neurosci. 1991;11: 3135–3145.
21. Lu J, Bjorkum AA, Xu M, Gaus SE, Shiromani PJ, Saper CB. Selective activation of the extended ventrolateral preoptic nucleus during rapid eye movement sleep. J Neurosci. 2002;22: 4568–4576.
22. Ko EM, Estabrooke IV, McCarthy M, Scammell TE. Wake-related activity of tuberomammillary neurons in rats. Brain Res. 2003;992:220–226.
23. Gallopin T, Luppi PH, Cauli B, Urade Y, Rossier J, Hayaishi O, Lambolez B, Fort P. The endogenous somnogen adenosine excites a subset of sleep-promoting neurons via A2A receptors in the ventrolateral preoptic nucleus. Neuroscience. 2005;134:1377–1390.
24. Gallopin T, Luppi PH, Rambert FA, Frydman A, Fort P. Effect of the wake-promoting agent modafinil on sleep-promoting neurons from the ventrolateral preoptic nucleus: An *in vitro* pharmacologic study. Sleep. 2004;27:19–25.
25. Saper CB, Chou TC, Scammell TE. The sleep switch: Hypothalamic control of sleep and wakefulness. Trends Neurosci. 2001; 24:726–731.
26. Schwartz JRS, Roth T. Neurophysiology of sleep and wakefulness: Basic Science and Clinical Implications. Curr Neuropharmacol. 2008;6:367–378.
27. National Institutes of Health. Revision of the NIH National Sleep Disorders 2003 Research Plan. Bethesda MD: National Institutes of Health; 2003.
28. Harsh JR, Hayduk R, Rosenberg R, Wesnes KA, Walsh JK, Arora S, Niebler GE, Roth T. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr. Med. Res. Opin. 2006; 22:761–774.
29. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437: 1257–1263.
30. Dunn AJ, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: Is CRF a mediator of anxiety or stress responses? Brain Res Brain Res Rev. 1990;15: 71–100.

31. Kato T, Montplaisir JY, Lavigne GJ. Experimentally induced arousals during sleep: A cross-modality matching paradigm. J Sleep Res. 2004;13:229–238.
32. Born J, Fehm HL. Hypothalamus-pituitary-adrenal activity during human sleep: A coordinating role for the limbic hippocampal system. Exp Clin Endocrinol Diabetes. 1998;106:153–163.
33. Steiger A, Guldner J, Knisatschek H, Rothe B, Lauer C, Holsboer F. Effects of an ACTH/MSH(4-9) analog (HOE 427) on the sleep EEG and nocturnal hormonal secretion in humans. Peptides. 1991;12: 1007–1010.
34. Axelsson J, Ingre M, Akerstedt T, Holmbäck U. Effects of acutely displaced sleep on testosterone. J Clin Endocrinol Metab. 2005;90:4530–4535.
35. Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, Selbie S, Belenky G, Herscovitch P. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain. 1997;120:1173–1197.
36. Renko AK, Hiltunen L, Laakso M, Rajala U, Keinänen- Kiukaanniemi S. The relationship of glucose tolerance to sleep disorders and daytime sleepiness. Diabetes Res Clin Pract. 2005;67:84–91.
37. Han SK, Kim L, Shim I. Stress and sleep disorder. Experimental Neurobiology. 2012;141–150.
38. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2011;162:CD007506.
39. Rotterdam ESHRE/ ASRM- Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81:19–25.
40. Lara HE, Ferruz JL, Luza S, Bustamante DA, Borges Y, Ojeda, SR. Activation of ovarian sympathetic nerves in polycistic ovary syndrome. Endocrinology. 1993; 133:2690-2695.
41. Zangeneh FZ, Mohammadi A, Ejtemaeimehr Sh, Naghizadeh MM, Fatemeh A. The role of opioid system and its interaction with sympathetic nervous system in the processing of polycystic ovary syndrome modeling in rat. Arch Gynecol Obstet. 2011;283:885-92.
42. Acuña E, Fornes R, Fernandois D, Garrido MP, Greiner M, Lara HE, Paredes AH. Increases in norepinephrine release and ovarian cyst formation during ageing in the rat. Reprod Biol Endocrinol. 2009;7:64.
43. Ter Horst JG, Wichmann R, Gerrits M, Westenbroek C, Lin Y. Sex differences in stress responses: Focus on ovarian hormones. Physiology & Behavior. 2009; 97:239-49.
44. Malyala A, Kelly JM, Rønnekleiv OK. Estrogen modulation of hypothalamic neurons: Activation of multiple signaling pathways and gene expression changes. Steroids. 2005;70:397-406.
45. Chen MD, O'Byrne KT, Chiappini SE, Hotchkiss J, Knobil E. Hypoglycemic 'stress' and gonadotropin-releasing hormone pulse generator activity in the rhesus monkey: Role of the ovary. Neuroendocrinology. 1992;56:666-73.
46. Rabine DS, Johnson EO, Liapi C, Chrousos GP. Glucocorticoids inhibit estradiol mediated uterine growth: Possible role of the uterine estradiol receptor. Biol Reprod. 1990;42:74-80.
47. Sakakura N, Takebe K, Nakagawa S. Inhibition of luteinizing hormone secretion induced by synthetic LRH by long-term treatment with glucocorticoids in human subgects. J Clin Endocrinol Metab. 1975; 40:774-9.
48. Roos C, Lidfeldt J, Agardh CD. Insulin resistance and self-rated symptoms of depression in Swedish women with risk factors for diabetes: The women's health in the Lund area study. Metabolism. 2007; 56:825–9.
49. Adali E, Yildizhan R, Kurdoglui M, Kolusari A, Edirne T, Sahin HG, et al. The relationship between clinicobiochemical characteristics and psychiatric distress in young women with polycystic ovary syndrome. The Journal of International Medical Research. 2008;36:1188–96.
50. Hirschberg AL. Polycystic ovary syndrome, obesity and reproductive implications. Womens Health (Lond Engl). 2009;5: 529-42.
51. Barnard L, Ferriday D, Guenther N. Quality of life and psychological wellbeing in polycystic ovary syndrome. Hum Reprod. 2007;22:2279–86.
52. Willmott J. The experiences of women with polycystic ovarian syndrome. Feminism Psychol. 2000;10:107-16.
53. Barry JA, Hardiman PJ, Saxby BK, Kuczmierczyk A. Testosterone and mood dysfunction in women with polycystic

ovarian syndrome compared to subfertile controls. J. Psychosom Obstet Gynaecol. 2011;32:104-11.

54. Kumarapeli V, Seneviratne Rde A, Wijeyaratne C. Health-related quality of life and psychological distress in polycystic ovary syndrome: A hidden facet in South Asian women. BJOG. 2011;118:319-28.
55. Sundararaman PG, Shweta, Sridhar GR. Psychosocial aspects of women with polycystic ovary syndrome from south India. J Assoc Physicians India. 2008;56: 945-8.
56. Zangeneh FZ, Naghizadeh MM, Abedinia N, Haghollahi F, Hesarehei D. Psychological signs in patients with polycystic ovary syndrome. Journal of Family and Reproductive Health. 2012; 6:145-153.
57. Zangeneh FZ, Naghizadeh MM, Jafarabadi M. Immune modulation of interleukin-1α by noradrenaline and cortisol in women with PCOS (Psychoneuroimmunology aspect). Annual Research & Review in Biology. 2015;7(6):390-398.
58. Zangeneh FZ, Naghizadeh MM, et al. Opioid system (β-endorphin) and stress hormones profiling in women with polycystic ovary syndrome. Annual Research & Review in Biology. 2015;5(5): 409-418.
59. Shreeve N, Cagampang F, Sadek K, Tolhurst M, Houldey A, Hil CM, Brook N, Macklon N, Cheong Y. Poor sleep in PCOS; is melatonin the culprit? Human Reproduction. 2013;28(5):1348-53.
60. Zangeneh FZ, Naghizadeh MM, Abdollahi A, Bagheri M. Synchrony between ovarian function & sleep in polycystic ovary syndrome patients. Open Journal of Obstetrics and Gynecology. 2014;4: 725-731.
61. Milutinović DV, Macut D, Božić I, Nestorov J, Damjanović S, Matić G. Hypothalamic-pituitary-adrenocortical axis hypersensitivity and glucocorticoid receptor expression and function in women with polycystic ovary syndrome. Experimental and Clinical Endocrinology & Diabetes. 2011;119:636-643.
62. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. International Journal of Obesity and Related Metabolic Disorders. 2002;26:883–896.
63. Vrbikova J, Hainer V. Obesity and polycystic ovary syndrome. Obesity Facts. 2009;2:26–35.
64. Jones GL, Hall JM, Balen AH, Ledger WL. Health-related quality of life measurement in women with polycystic ovary syndrome: A systematic review. Human Reproduction Update. 2008;14:15–25.
65. Frène VD, Verhofstadt L, Lammertyn J, Stuyver I, Buysse A, Sutter PD. Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program. JOGNN. 2015;44:587–599.
66. Liao LM, Nesic J, Chadwick PM, Brooke-Wavell K., Prelevic GM. Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: A pilot investigation. Gynecological Endocrinolog. 2008;24:555–561.
67. Galletly C, Moran L, Noakes M, Clifton P, Tomlinson L, Norman R. Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome – A pilot study. Appetite. 2007;49:590–593.

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