Journal of Biology and Today's World

Journal home page: http://journals.lexispublisher.com/jbtw

Received: 12 May 2017 • Accepted: 08 July 2017

Review

doi:10.15412/J.JBTW.01060802

Polycystic Ovary Syndrome and Sympathoexcitation: Management of Stress and Lifestyle

Farideh Zafari Zangeneh*

Vali-e-Asr, Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran, Iran

*Correspondence should be addressed to Farideh Zafari Zangeneh, Vali-e-Asr, Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran, Iran; Tel: +982166581616; Fax: +982166581658; Email: Zangeneh14@gmail.com.

ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous disease with unknown etiology, a scientific challenge for researchers and is often a complex condition to manage for clinicians. Life exists by maintaining a complex dynamic equilibrium or homeostasis that is constantly challenged by intrinsic or extrinsic adverse forces, the stressors. Stress reactivity is markedly influenced by both pubertal maturation and the experience in the individual. For example, chronic stress destroys bodies, minds and lives. Chronic stress kills through suicide, violence, heart attack, stroke, and cancer. Much evidence suggests that women with PCO often at risk for secondary complications of this syndrome including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life). The relationships between the psychological health aspects and the clinical characteristics of PCOS are not yet clear. In this review, we investigate the key roles of corticotrophin-releasing hormone (CRH) and norepinephrine (NE) in orchestrating the response to stress in women with PCOS.

Key words: Polycystic ovary syndrome (PCOS), Norepinephrine (NE), CRH, Chronic stress, Life style.

Journal of Biology and Today's World is published by *Lexis Publisher*; Journal p-ISSN 2476-5376; Journal e-ISSN 2322-3308.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common problem encountered by young pubertal girls (1). PCOS is a constellation of risk factors such as menstrual irregularities, polycystic ovaries, acne, hirsutism and increased obesity, "all likely to impact quality of life and mood and potentially precipitate depression and anxiety" (2). PCO as the chronic disease is a known risk factor for central obesity (3), cardiovascular disease (CVD) (4), type 2 diabetes mellitus (5), cancer (6), infertility (7) and psychological disorders (8). The pathogenesis is complicated but interaction of genetic factors, obesity, dietary and sedentary lifestyle is known to contribute towards the development of the disease (9). The linkage between clinical features of PCO and reduced quality of life in these women was frequently suggested in several researches (10, 11). There are many reports that show how physical symptoms can cause mental disorders, obesity and infertility as the most frequent symptoms in women with PCOS seem to be independent of depression and anxiety (12).

1. Pathogenesis of PCOS

In the pathogenesis of PCOS, hyperandrogenism and insulin resistance (IR) are the endocrine cornerstones which could explain the various symptoms of the metabolic disorders. Follicle growth is disturbed by hyperandrogenism, resulting in a large number of small follicles and the increasing of stroma due to enhanced follicle atresia (13). Infertility as a result of this disorder has been shown in these women (14). In 2014 Hung et al explored the relationship between PCOS and the subsequent development of psychiatric disorders including schizophrenia, bipolar disorder, depressive disorder, anxiety disorder, and sleep disorder. They reported that "the incidence of depressive, anxiety and sleep disorder were higher among the PCOS patients than among the patients in the comparison cohort" (15). The report of Yu et al., in 2016 showed that dehydroepiandrosterone (DHEA)-induced PCOS mice, "exhibited depression-like behavior according to the results from behavioral assessment. The brain contents of monoamines and/or their

metabolites decreased in DHEA-treated mice compared with controls". They suggested that the down-regulation of brain monoamines and their metabolites which implies the contribution of hyperandrogenism to the psychological symptoms of women with PCOS (16).

2. PCO modeling in rat

Lara and colleagues showed that catecholamine homeostasis can be changed by a single dose of estradiol valerate (EV) in rats (17, 18). There was an elevation of norepinephrine (NE), down-regulation of β2-adrenoceptor (β2 AR) in granulosa and theca-interstitial cells (19) and an increase of nerve growth factor (NGF) in rat's ovary (20). Bernuci et al, in 2008 and 2013, demonstrated the major role of NE in the development of ovarian cysts in rats that were exposed to cold stress for four weeks. Lesion of locus coeruleus nucleus (LC) could reduce NE activity in rat ovary to cold stress (21, 22).

3. PCOS & Catecholamine (monoamines) System

The autonomic nervous system (ANS) include: sympathetic and parasympathetic nervous systems controls a wide range of functions, include: gastrointestinal, cardiovascular, respiratory, renal, endocrine and other systems are regulated by sympathetic autonomic system (SAS) and the parasympathetic system, or both (23). The orchestrating role of catecholamine in response to stress in the brain can be the main axis of metabolic and psychologic disorders in PCOS. Frequent or prolonged stress may lead to a maladaptive state for a wide range of diseases by increasing the allosteric load. Influence of catecholamine depends on the nature of the stressor (24) and availability of the adrenal steroids (25). In the central nervous system (CNS), a variety of stressors increase norepinephrine (NE) biosynthesis in sympathetic ganglia and the LC (26). Many findings suggest that estradiol (E2) has a positive feedback action on the release of luteinizing hormone (LH) E2 by NE from the LC (27). Our work in 2012 suggested the critical role of NE neurons in LC on the feedback system of estradiol. Lesion of LC in PCO rats could increase estradiol level and induce hyperthecosis of ovary (28). LC/NE system is a collection of noradrenergic neurons in the brain stem. LC/NE actives hypothalamic-pituitary-adrenal (HPA) axis by neuroendocrine responses to stress conditions (29). In 2015, we reported that adrenaline in the serum of women with PCOS is higher than control group (30), and many findings show that there is hyperactivity of HPA axis and SNS in this syndrome.

4. PCOS, HPA and corticotrophin releasing hormone (CRH)

The female reproductive system is regulated by the hypothalamic-pituitary-ovary (HPO) axis. Corticotrophin releasing hormone (CRH), arginine-vasopressin (AVP) and CRH/AVP are the principal regulators of HPA axis that can synergistically stimulate ACTH and cortisol secretion by cortex of the adrenal gland (31). GnRH is another regulator of HPA axis that stimulates LH and FSH secretion from pituitary gland and subsequently, progesterone and estradiol will be released by the ovary (32). Activation of the HPA by stress exerts an inhibitory effect on the female reproductive system. CRH can inhibit the secretion of GnRH from the hypothalamus (33). CRH is a strong regulator of the autonomic nervous system (ANS) and behavioral effects of stress. CRH is involved in inflammatory and steroidogenesis processes in ovary (34). The secretion of CRH from neurons of sensory afferent and postganglionic sympathetic nervous system regulates the inflammation processes in testis, ovary, endometrium and placenta (35, 36). CRH plays a major role in ovulation, luteolysis, implantation and parturition that are component of inflammatory processes in female reproductive system (37). The anti-reproductive action of CRH in ovary of women with high psychosocial stress may be lead to earlier ovarian failure (38).

5. Stress

5.1. Stress as the part of daily life

Nowadays, the normal part of everyday living is stress. Hans Selye in 1936 proposed general adaptation syndrome (GAS). He suggested there are three stages for the body in response to stress: 1) the alarm reaction or SNS response to stress as fight or flight; 2) the resistance to stress and 3) the duration of stress. The physiological response to stress is the maintaining of stability or homeostasis in body. The long-term activation of the stress system in body is serious and can even be lethal (31). Hans Sely suggested that stressors can disturb homeostasis stable of body include mental and psychology or sociologic. These stressors can directly to the production of disease or increase the risk of disease. The disruption and maintaining process of homeostasis is termed *allostatic status*. Inevitably, this situation could enable a wide field of physiological and behavioral mechanisms. The stressors as the intrinsic or extrinsic adverse forces can constantly challenge the homeostasis or dynamic equilibrium of internal environment of body (31). The organism must activate restraining forces during stress, because these forces are essential for successful adaptation. The general adaptation is the only way for acting of stress. This adaptation can cause defense or damage. Stress response must occur quickly, if the response delays, the "adaptive changes may turn excessive, prolonged, and maladaptive and thus contribute to the development of pathologic processes" (39). Stress-associated disorders subdivided in two categories: 1) Stress-associated with activation of stress system, including depression and anxiety. 2) Stress-associated with decreased stress system activity, such as atypical depression and posttraumatic stress disorder (PTS) (40) these are representative disorder stress-associated with psychological and/or physical stressors in the daily life.

5.2. Brain & stress

Brain is a main target for stress. Hypothalamus is the important region of the brain for neuroendocrine responses that are recognized as the target of stress adaptation. "Early life events influence life-long patterns of emotionality and stress responsiveness and alter the rate of brain and body aging. The hippocampus, amygdala, and prefrontal cortex undergo stress-induced structural remodeling, which alters behavioral and physiological responses". As an adjunct to pharmaceutical therapy, social and behavioral interventions such as regular physical activity and social support reduce the chronic stress burden and benefit brain and body health and resilience (41). Stress system includes response and adaptation and transient adaptation is allostatic load. Activation of hypothalamus-pituitary-adrenal (HPA) and sympathoadrenal responses to stress promote transient adaptation and maintenance in the short-term. The response pattern of HPA and autonomic nervous system to stress is directly dependent on the type of stress (42).

5.3. Stress system

5.3.1. Stress syndrome &brain nuclei

Hypothalamus and brain stem are the central area for stress system. This nuclear collection composed of parvocellular, paraventricular nuclei (PVN) of the hypothalamus and parabranchial, paragigantocellular nuclei of the medulla and locus ceruleus (LC) as the LC-noradrenergic cell groups of the medulla and pons (LC/NE) (42, 43).

5.3.2. Stress syndrome physiology

The stress cascade or stress response is the activation of sympathetic nervous system (SNS) and HPA axis, is accompanied with the series of neurological and endocrine glands signals (44)."The stress cascade is responsible for allowing the body to make the necessary physiological and metabolic changes required to cope with the demands of a homeostatic challenge" (45).

5.3.3. Regulation of the stress response & CRH

Several neurotransmitter systems orchestrate the characteristic phenomenology of autonomic, endocrine, immune, behavioral (psychological) responses to stress (46). Intracerebroventricular administration of corticotrophin releasing hormone (CRH) antagonists can suppress many behavioral of the stress response. CRH receptors are widely distributed in the Hypothalamus, Limbic system and the central arousal sympathetic systems (LC/NE) in the brain stem and spinal cord (47, 48). CRH is the strongest neurotransmitter from the hypothalamus and extra hypothalamic sites (48).

5.3.4. Regulation of the stress response & NE

The LC/NE system is the collection of locus coeruleus and other noradrenergic cell groups from pons and medulla oblongata of the midbrain. Epinephrine as an alarm system in brain can decreases neurovegetative functions, like sleeping and eating and activates HPA axis and the autonomic and neuroendocrine responses to stress. In brain the reciprocal connections between two systems LC/NE and CRH show that CRH and norepinephrine (NE) are stimulator of the other (49) and the credibility of this system is the hemostasis of feedback loop of them. "There is an ultra-short auto regulatory negative feedback loop on the CRH neurons exerted by CRH itself, just as there is a similar loop in the LC/NE neurons, by way of presynaptic CRH and noradrenergic receptors, respectively" (50). Gonadal axis function can be suppressed with glucocorticoids at the central level in hypothalamic, pituitary and at peripheral in uterine level (51). Mastorakos et al showed the significantly reduction of the peak luteinizing hormone response to intravenous GnRH by administration of glucocorticoid that suggesting an inhibitory effect of glucocorticoids on the pituitary gonadotroph (52). These studies confirmed that the main regulators of hypothalamic pituitary ovary (HPO) axis are CRH and GnRH that stimulates FSH and LH secretion and subsequently, estradiol and progesterone secretion by the ovary. The local circuitry neurons such as proopiomelanocortin (POMC) and the neurosecretory neurons such as dopamine and GnRH neurons are the hypothalamic target neurons for estrogen (Figure 1) (32, 38).

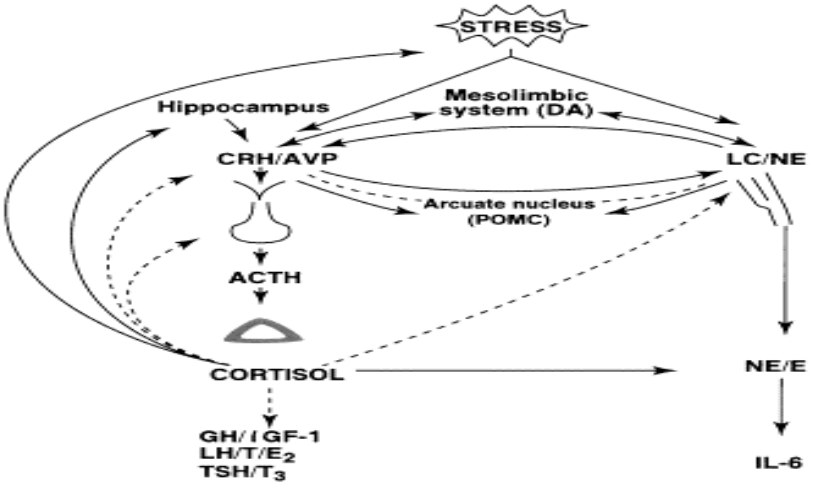

Figure 1. "The HPA axis is controlled by several feedback loops that tend to normalize the time-integrated secretion of cortisol, yet glucocorticoids stimulate the fear centers in the amygdala. A simplified schematic representation of the central and peripheral components of the stress system, their functional interrelations and their relations to other central systems involved in the stress response. The CRH/AVP neurons and central catecholaminergic neurons of the LC/NE system reciprocally innervate and activate each other. The HPA axis is controlled by several feedback loops that tend to normalize the time-integrated secretion of cortisol, yet glucocorticoids stimulate the fear centers in the amygdala. Activation of the HPA axis leads to suppression of the GH/IGF-1, LH/testosterone/E2 and TSH/T3 axes; activation of the sympathetic system increases IL-6 secretion. Solid lines indicate stimulation; dashed lines indicate inhibition" (38).

5.4. Stress system & Time course of neural effects of stress

Psychological stress can be defined by four characteristics: novelty, uncertainty, uncontrollability and social self (e.g., status, reputation). These characteristics cause to release the stress neurohormones. Rapid phase of stress neural effects is the activation of SAS and release of catecholamine. Slow phase is the release of glucocorticoids by activation of HPA axis "with cortisol levels peaking at 20-40 min following stressor onset" (53). Hippocampus and HPA axis are two important locations for long term potentiation (LTP) shortly after stress exposure (54). LTP formation on memory determines the type of stress. Time course of neural effects of stress is the main axis of stress management. There are three types of stress in duration.

5.5. Different types of stress

Stress management can be complicated and confusing because there are different types of stress: acute stress, episodic acute stress, and chronic stress, each with its own characteristics, symptoms, duration, and treatment approaches:

5.5.1. Acute Stress

Acute stress reaction can be called acute stress disorder (ASD) or psychological (mental) shock is the common form of stress. In the 1920s, Walter Cannon suggested that acute stress associated with a general discharge of the sympathetic nervous system (SNS). Symptoms of acute stress may take 2-30 days. If symptoms persist, it could lead to post-traumatic stress disorder (PTSD) (55).

5.5.2. Episodic Acute Stress

Over the past decades, research on episodic memory and the effect of stress show that emotional arousal increases the episodic memory. The link of basolateral amygdala (BLA) and catecholamine can modulate the processes of acquisition and consolidation in the medial temporal lobe (MTL) (56). Glucocorticoids have the main role in the formation of memory retrieval of episodic acute stress.

5.5.3. Chronic Stress

Hans Selye (1907–1982), known as the father of stress, described that acute stress can be exciting and thrilling, while chronic stress is not. Chronic stress can markedly increase the vulnerability to adverse medical outcomes. Studies on chronic stress have prompted scientists to advance numerous theories over the past 50 years for linking of stressors, cortisol and disease (57). As mentioned above, the main mechanism for adaptation of acute stress is the co-regulation of LC/NE system with CRH, however, prolonged or hypersecretion can lead to chronic stress (Figure 2) (30, 58).

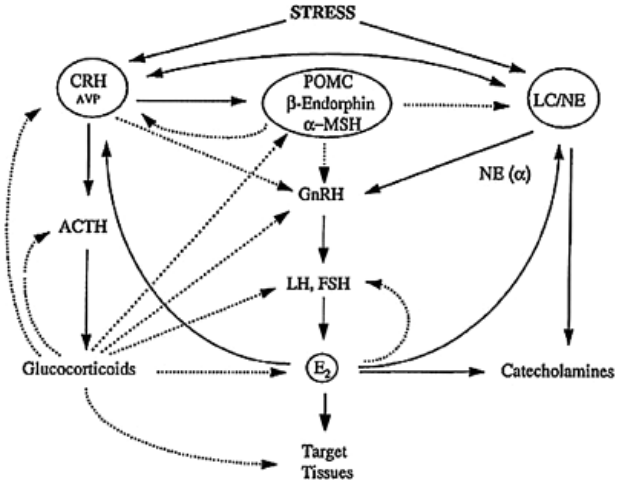

Figure 2. Heuristic representation of the interplay among the HPA axis, the locus ceruleus/norepinephrine (LC/NE) system. The dotted lines represent inhibition while the solid lines represent stimulation (30).

5.6. Chronic stress & Reproductive system

CRHR-1 receptors have been identified in granulosa, theca and cumulus oophorus cells of the graafian follicle. Reproductive CRH with together immunity system participates in different levels of reproductive functions, like: ovulation, luteolysis, implantation and parturation (59). The link of CRH for the processes of follicular atresia and luteolysis may be done by autocrine and paracrine mechanismes for steroidogenesis and follicular maturation (60).

6. Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS), the most common female endocrine disorder, is a complex and heterogenic disease. The etiology of PCOS is unknown although abnormalities in steroidogenesis (the production of steroid hormones such as reproductive hormones) and gonadotrophin action (the action of hormones that control reproductive hormone production) are implicated. Insulin resistance and compensatory hyperinsulinemia are proposed as significant etiological factors and are present in a high proportion of both lean and overweight women with PCOS (61). The first community-based study of PCOS prevalence using Rotterdam criteria was based in Australia and showed that 17.8% of women have PCOS (62). The human ovary has a functional sympathetic innervation. The relationships between the psychological health aspects and the clinical characteristics of PCOS are not yet clear.

6.1. PCOS & Insulin resistance: CRH/SAS and insulin resistance (IR)

Cortisol dysregulation has been proposed to be involved in depression. Hypothalamic–pituitary–adrenal (HPA) axis dysregulation associated with major depressive disorder (MDD) was previously reported to be higher in the elderly (63). Furthermore, IR and the prevalence of type 2 diabetes are known to increase with aging (64). Although previous studies demonstrated that depression indirectly influenced the physical health of the elderly through cognitive impairments and social factors such as a lower income and poor social support (65), depression, per se, may directly affect the physical health of the elderly through insulin resistance and type 2diabetes. From a clinical perspective, clinicians should consider the risk of type2 diabetes when they treat elderly MDD patients (64). Landsberg in 1983 proposed that central insulin resistance contributes to elevated sympathetic outflow by increased insulin-mediated glucose metabolism in hypothalamic neurons, leading to suppression of the inhibitory pathway between the hypothalamus and brainstem sympathetic centres (66). Sympathetic hyperactivity may also contribute to increased insulin resistance. Masuo et al, in 2003 showed that baseline plasma norepinephrine levels independently predicted a rise in BMI, blood pressure and hyperinsulinemia in their 5-year longitudinal study of 433 young, no obese, normotensive men (67). The relationship between sympathetic activity and insulin resistance would thus appear to be complex and bidirectional (63).

6.2. PCOS & Obstructive sleep apnea

Obstructive sleep apnea (OSA) is an established risk factor for cardiovascular disease and is associated with a greater risk of insulin resistance and type2 diabetes. Compared with age- and weight-matched controls, women with PCOS have an increased risk of OSA, which occurs in 44–70% of obese patients with the syndrome (68, 69) OSA correlates significantly with insulin resistance and glucose intolerance in patients with PCOS (70). Sympathetic over activity is thus postulated as an important mechanism by which OSA increases the risk of cardiovascular disease and, importantly, this can be reduced by treatment with continuous positive airways pressure(CPAP) (71).

6.3. PCOS & chronic stress

In general, acute, transient challenges that trigger active (fight or flight) adaptation produce a short-term response referred to as the defense reaction consisting primarily of sympathoadrenal activation. In stressfull situation, the activity of HPA axis, LC- NE system and inhibitory tone

of opiates increase and this significant deactivation in μ-opioid neurotransmission, can result in overactivity of SNS and increase gene expression and elevate TH mRNA levels in response to stress. When the magnitude of the stressors reaches a certain threshold, there is activation of the stereotyped adaptive response, the general adaptation or stress syndrome. In adaptation of stress the hyperactivity of SNS, hyperresponsivness of the LC-NA system and co-regulation of LC-NA system by CRH and opioids can disrupt this balance especially in LC. Studies show that LC activation is necessry for depolarization of LHRH neurons and consequent LH surge (66). Further research is needed to clarify the central SAS (LC/NE) and intraovarian neurotrophin-mediated sympathetic activations of stress in female reproductive system. It is principal brain effectors are the Paraventricular nucleus (PVN) neurons synthesizing CRH and the Locus ceruleus norepinephrine neurons. 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 (72). Acting together, these two neuronal groups initiate an adaptation response that includes improved alertness and attention span, decreased reflex time, antinociception, suppression of feeding and sexual behavior and activation of the sympathoadrenal and HPA systems. These transient allostatic responses are adaptive and result in energy mobilization, increased traffiking of immune cells and promotion of memory storage (due to effect of glucocorticoids in the hippocampus). In normal conditions, this allostatic response is shut off during the recovery after stress. In contrast, chronic stress states produce anxiety and passive or withdraval coping mechanisms elicit a long-term response reffered to as the vigilance or defeat reaction characterized by chronic activation of HPA system. The consequences of overactivity of the allostatic load and accure in 4 main settings: 1) chronic stress due to repeated hits by multiple novel stressors; 2) lack of adaptation to repetition of the same stressors; 3) prolonged response due to inability to shut down the allostatic response; and 4) inadequate response, leading to compensatory hyperactivity of other systems. Allostatic load is maladaptive and leads to obesity,diabetes, hypertension, muscle wasting, increased susceptibility to infection and impairment of memory (from damaging effects of chronically elevated glucocorticoid values on hippocampal cells) (73). Increased of CRH and beta-End in the hypothalamus and also the tonic inhibitory effect of beta-End on sympathetic tone in stressful situations (74), inhibits the secretion of gonadotropins, oxytocin and vasopressin ,this may lead to amenorrhea ,which often is a consequence of intensive training or psychological stress (75) and can disrupt parturition and lactation (76). Accordingly, impaired follicular development appears to be the most common cause of reproductive dysfunction attributable to stress in the humans female (77). The reduction in endogenouse GnRH/LH secretion utility deprives the ovarian follicular of adequiate gonadotropin support leading to reduced oestradiol production by slower growing follicules. These studies show that there is a level of interference by stressors at the ovary (78). Intrestingly, several components of the HPA axis and their receptors are present in reproductive tissues as autacoid regulators of their various function.These include ovarian and endometrial CRH, which may participate in the inflammatory processes of the ovary estrogen directly stimulates the CRH gene, which may explain the slight hypercortisolism of female and the proponderance of depressive anxiety and eating disorders as well as cushing disease in women (79). PCO present diminished amounts of CRH immunoreactivity, suggesting that decreased ovarian CRH might be related to the anovulation of PCO (52). CRH activates LC neurons directly even when synaptic activity is prevented. This direct action is consistent with ultra-structural evidence for synaptic contacts between CRH-immunoreactive terminals and LC dendrites (80). Furthermore; increased levels of CRH within the LC of depressed patients have recently been reported (81). The pattern collaboration between CRH and LC-NA in HPA axis of women reproduction system is very complex and disruptions in the feedback systems can trigger ovarian dysfunction.

7. Lifestyle and Quality of Life in women with PCOS

Lifestyle factors play an important role and dramatic impact on public health and capacity for reproduction and fertility. Unlike everyday stressors, which can be managed with healthy stress management behaviors, untreated chronic stress can result in serious health conditions including anxiety, insomnia, muscle pain, high blood pressure and a weakened immune system (82). Research has shown that chronic stress can be treated with appropriate interventions such as lifestyle and behavior change, therapy, and in some situations, medication (41).

7.1. Diet

Eating a healthy diet consisting of appropriate composition and caloric intake is fundamental to maintaining a state of optimum physical and psychological health. It is also important in preventing diseases such as obesity, cardiovascular disease, diabetes, osteoporosis and some cancers. Diet mediates body weight and composition and should be considered fundamental to reproduction (83).

7.2. Exercise

Rich-Edwards et al. in 2002 reported that exercise was associated with a reduction in risk of ovulatory infertility. After adjustment for BMI, each hour of vigorous exercise per week was associated with a relative risk reduction of 5%, suggesting that physical activity may protect ovarian functioning independent of BMI (84). It is reasonable to assume that the general health benefits associated with moderate levels of exercise and the consumption of a well-balanced diet would also apply to fertility. These lifestyle

practices should therefore be recommended to couples attempting pregnancy. However, there is a need for further research regarding the effects that moderate and low-level exercise may have on reproductive performance.

7.3. Sleep

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 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 (85). 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., 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 (86). 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. Only cortisol has significant relation with PSQI global score by regression analysis and it associated with time of sleep (87). 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.

8. Managing the stress

Psychological stress may reduce female reproductive performance in various ways. The autonomic nervous system, the endocrine and immune systems have all been implicated (87-89). Studies over the past decade show that individual lifestyle can be helpful in the treatment of polycystic ovary. The most effective way to manage the stress is to practice a lifestyle suited to each individual environment. Our results by using of demographic and sleep (PSQI) questionnaires showed that 98% of women with PCOS were housewives and the average sleep times were twelve midnight until ten in the morning (Table 1).

Table 1. Comparison of age, PSQI scores and Hormones in study groups

P-value T test	PCOS (N = 77) Mean ± SD	Control (N = 97) Mean ± SD	Variables
<0.001	26.6 ± 4.7	29.6 ± 5.2	**Age (year)**
0.935	7.0 ± 4.1	6.9 ± 4.4	**Marital Duration (year)**
			PSQI Scores
0.673	5.16 ± 2.33	5.00 ± 2.48	Total Score (0 - 21)
0.253	1.10 ± 0.58	1.16 ± 0.49	Sleep Quality (0 - 3)
0.455	1.78 ± 1.13	1.65 ± 1.18	Sleep onset latency (0 - 3)
0.796	0.25 ±0.6	0.19 ± 0.53	Sleep duration (0 - 3)
0.641	0.12 ± 0.40	0.09 ± 0.38	Sleep efficacy (0 - 3)
0.419	0.97 ± 0.36	0.93 ± 0.3	Sleep disturbance (0 – 3)
0.169	0.04 ± 0.34	0.13 ± 0.61	Using sleeping medication (0 - 3)
0.679	0.90 ± 0.80	0.85 ± 0.80	Daytime dysfunction (0 - 3)
0.031	25.48 ± 15.99	32.45 ± 24.27	**Hormones**
0.652	190.57 ± 75.07	197.08 ± 106.89	Melatonin (pg ml^{-1})
<0.001	81.58 ± 10.19	87.19 ± 9.39	Cortisol (ng ml^{-1})
0.982	2.22 ± 3.24(0.80)	3.79 ± 7.73	β-endorphin (pg ml^{-1})
<0.001	5.97 ± 4.49 (5.00)	3.61 ± 3.11(3.10)	Progesterone (mg ml^{-1})
0.737	0.50 ± 1.35 (0.00)	0.74 ± 3.38 (0.00)	Adrenalin (ng ml^{-1})
			Noradrenalin (ng ml^{-1})

Insufficient sleep can have adverse effects on stress hormones release (cortisol and catecholamine). Future research about sleep in PCO women should register other sleep dimensions (sleep patterns or disturbances) to provide a better insight in this scientific field.

9. CONCLUSION

Lifestyle is essential for the physiological homeostasis. When physiological homeostasis established stress management is possible. Removal of stress can normalize

the activity of the HPA axis. This normalization improves the performance of the reproductive system. So clearly Lifestyle can have a potential role for managing of stress.

ACKNOWLEDGMENT

Not mentioned any acknowledgment by authors.

FUNDING/SUPPORT

This review is the result of an original study that was supported with funding of the Research Council of Tehran University of Medical Sciences; Tehran, Iran supported this study by a grant publication No. 30365, revised 2016.

AUTHORS CONTRIBUTION

Not applicable.

CONFLICT OF INTEREST

The author (s) declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

REFERENCES

1. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. Clinical endocrinology. 2000;52(5):595-600.
2. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. Fertility and sterility. 2010;93(7):2421-3.
3. Lim S, Davies M, Norman R, Moran L. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Human reproduction update. 2012;18(6):618-37.
4. Scicchitano P, Dentamaro I, Carbonara R, Bulzis G, Dachille A, Caputo P, et al. Cardiovascular risk in women with PCOS. International journal of endocrinology and metabolism. 2012;10(4):611.
5. Delitala AP, Capobianco G, Delitala G, Cherchi PL, Dessole S. Polycystic ovary syndrome, adipose tissue and metabolic syndrome. Archives of Gynecology and Obstetrics. 2017:1-15.
6. Kim J, Mersereau JE, Khankari N, Bradshaw PT, McCullough LE, Cleveland R, et al. Polycystic ovarian syndrome (PCOS), related symptoms/sequelae, and breast cancer risk in a population-based case–control study. Cancer Causes & Control. 2016;27(3):403-14.
7. Melo AS, Ferriani RA, Navarro PA. Treatment of infertility in women with polycystic ovary syndrome: approach to clinical practice. Clinics. 2015;70(11):765-9.
8. Scaruffi E, Gambineri A, Cattaneo S, Turra J, Vettor R, Mioni R. Personality and psychiatric disorders in women affected by polycystic ovary syndrome. Frontiers in endocrinology. 2014;5.
9. Amato P, Simpson JL. The genetics of polycystic ovary syndrome. Best practice & research Clinical obstetrics & gynaecology. 2004;18(5):707-18.
10. Yanan Li M, Li Y, Ng EHY, Stener-Victorin E, Hou L, Wu T, et al. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis.
11. Hahn S, Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, et al. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. European journal of endocrinology. 2005;153(6):853-60.
12. Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. Human Reproduction. 2011;26(9):2442-51.
13. Webber LJ, Stubbs S, Stark J, Trew GH, Margara R, Hardy K, et al. Formation and early development of follicles in the polycystic ovary. Lancet (London, England). 2003;362(9389):1017-21.
14. Ehrmann DA. Polycystic ovary syndrome. The New England journal of medicine. 2005;352(12):1223-36.
15. Hung J-H, Hu L-Y, Tsai S-J, Yang AC, Huang M-W, Chen P-M, et al. Risk of psychiatric disorders following polycystic ovary syndrome: a nationwide population-based cohort study. PloS one. 2014;9(5):e97041.
16. Yu Q, Hao S, Wang H, Song X, Shen Q, Kang J. Depression-Like Behavior in a Dehydroepiandrosterone-Induced Mouse Model of Polycystic Ovary Syndrome. Biology of reproduction. 2016;95(4):79, 1-10.
17. Lara H, Ferruz J, Luza S, Bustamante D, Borges Y, Ojeda S. Activation of ovarian sympathetic nerves in polycystic ovary syndrome. Endocrinology. 1993;133(6):2690-5.
18. Lara H, Dorfman M, Venegas M, Luza S, Luna S, Mayerhofer A, et al. Changes in sympathetic nerve activity of the mammalian ovary during a normal estrous cycle and in polycystic ovary syndrome: Studies on norepinephrine release. Microscopy research and technique. 2002;59(6):495-502.
19. Barria A, Leyton V, Ojeda SR, Lara HE. Ovarian steroidal response to gonadotropins and beta-adrenergic stimulation is enhanced in polycystic ovary syndrome: role of sympathetic innervation. Endocrinology. 1993;133(6):2696-703.
20. Stener-Victorin E, Ploj K, Larsson B-M, Holmäng A. Rats with steroid-induced polycystic ovaries develop hypertension and increased sympathetic nervous system activity. Reproductive Biology and Endocrinology. 2005;3(1):44.
21. Bernuci MP, Szawka RE, Helena CV, Leite CM, Lara HE, Anselmo-Franci JA. Locus coeruleus mediates cold stress-induced polycystic ovary in rats. Endocrinology. 2008;149(6):2907-16.
22. Bernuci M, Leite C, Barros P, Kalil B, Leoni G, Bianco-Borges D, et al. Transitory Activation of the Central and Ovarian Norepinephrine Systems During Cold Stress-Induced Polycystic Ovary in Rats. Journal of neuroendocrinology. 2013;25(1):23-33.
23. Chrousos GP, Gold PW. A healthy body in a healthy mind--and vice versa--the damaging power of "uncontrollable" stress. The Journal of clinical endocrinology and metabolism. 1998;83(6):1842-5.
24. Gaillet S, Lachuer J, Malaval F, Assenmacher I, Szafarczyk A. The involvement of noradrenergic ascending pathways in the stress-induced activation of ACTH and corticosterone secretions is dependent on the nature of stressors. Experimental brain research. 1991;87(1):173-80.
25. Feuvrier E, Aubert M, Mausset AL, Alonso G, Gaillet S, Malaval F, et al. Glucocorticoids provoke a shift from alpha2- to alpha1-adrenoreceptor activities in cultured hypothalamic slices leading to opposite noradrenaline effect on corticotropin-releasing hormone release. Journal of neurochemistry. 1998;70(3):1199-209.
26. Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. Journal of psychosomatic research. 2002;53(4):865-71.
27. Gilbey MP, Spyer KM. Essential organization of the sympathetic nervous system. Bailliere's clinical endocrinology and metabolism. 1993;7(2):259-78.
28. Zangeneh FZ, Abdollahi A, Aminee F, Naghizadeh MM. Locus coeruleus lesions and PCOS: role of the central and peripheral sympathetic nervous system in the ovarian function of rat. Iranian journal of reproductive medicine. 2012;10(2):113.
29. Berridge CW, Waterhouse BD. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Research Reviews. 2003;42(1):33-84.
30. Zangeneh F, Naghizadeh M, Abdollahi A, Abedinia N. Opioid System ([beta]-endorphin) and Stress Hormones Profiling in Women with Polycystic Ovary Syndrome. Annual Research & Review in Biology. 2015;5(5):409.
31. Chrousos GP. Regulation and dysregulation of the hypothalamic-pituitary-adrenal axis. The corticotropin-releasing hormone perspective. Endocrinology and metabolism clinics of North America. 1992;21(4):833-58.
32. Malyala A, Kelly MJ, Rønnekleiv OK. Estrogen modulation of hypothalamic neurons: activation of multiple signaling pathways and gene expression changes. Steroids. 2005;70(5):397-406.
33. Rabin DS, Johnson EO, Brandon DD, Liapi C, Chrousos GP. Glucocorticoids Inhibit Estradiol-Mediated Uterine Growth: Possible Role of the Uterine Estradlol Receptor. Biology of reproduction. 1990;42(1):74-80.
34. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nature Reviews Neuroscience. 2009;10(6):397-409.
35. Kiapekou E, Zapanti E, Mastorakos G, Loutradis D. Update on the role of ovarian corticotropin-releasing hormone. Annals of the New York Academy of Sciences. 2010;1205:225-9.
36. Zangeneh F, Naghizadeh M, Bagheri M, Jafarabadi M. Are CRH & NGF as psychoneuroimmune regulators in women with polycystic ovary syndrome? Gynecological Endocrinology. 2017;33(3):227-33.
37. Kalantaridou SN, Makrigiannakis A, Zoumakis E, Chrousos GP. Stress and the female reproductive system. Journal of reproductive immunology. 2004;62(1-2):61-8.
38. Zangeneh FZ. Stress and female reproductive system: disruption of corticotropin-releasing hormone/opiate balance by sympathetic nerve traffic. Journal of Family and Reproductive Health. 2009;3(3):69-76.
39. Bernard C. An Introduction to the Study of Experimental Medicine: Dover Publications; 2012.
40. Selye H. A syndrome produced by diverse nocuous agents. 1936. The Journal of neuropsychiatry and clinical neurosciences. 1998;10(2):230-1.
41. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Annals of the New York Academy of Sciences. 2004;1032(1):1-7.
42. Chrousos GP, Gold PW. The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. Jama. 1992;267(9):1244-52.
43. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005;67:259-84.
44. Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stress. Endocrinology and Metabolism Clinics. 2001;30(3):695-728.
45. Tsigos C, Kyrou I, Kassi E, Chrousos GP. Stress, Endocrine Physiology and Pathophysiology. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al., editors. Endotext. South Dartmouth MA: MDText.com, Inc.; 2000.
46. Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. Annals of the New York Academy of Sciences. 1998;851:311-35.
47. Shibasaki T, Imaki T, Hotta M, Nicholas L, Demura H. Psychological stress increases arousal through brain corticotropin-releasing hormone

without significant increase in adrenocorticotropin and catecholamine secretion. Brain research. 1993;618(1):71-5.
48. Aguilera G, Liu Y. The molecular physiology of CRH neurons. Frontiers in neuroendocrinology. 2012;33(1):67-84.
49. Gaillet S, Lachuer J, Malaval F, Assenmacher I, Szafarczyk A. The involvement of noradrenergic ascending pathways in the stress-induced activation of ACTH and corticosterone secretions is dependent on the nature of stressors. Experimental brain research. 1991;87(1):173-80.
50. Chrousos GP. Organization and integration of the endocrine system: the arousal and sleep perspective. Sleep medicine clinics. 2007;2(2):125-45.
51. Sakakura M, Takebe K, Nakagawa S. Inhibition of luteinizing hormone secretion induced by synthetic LRH by long-term treatment with glucocorticoids in human subjects. The Journal of clinical endocrinology and metabolism. 1975;40(5):774-9.
52. Mastorakos G, Scopa CD, Kao LC, Vryonidou A, Friedman TC, Kattis D, et al. Presence of immunoreactive corticotropin-releasing hormone in human endometrium. The Journal of clinical endocrinology and metabolism. 1996;81(3):1046-50.
53. Gagnon SA, Wagner AD. Acute stress and episodic memory retrieval: neurobiological mechanisms and behavioral consequences. Annals of the New York Academy of Sciences. 2016;1369(1):55-75.
54. Joëls M, Krugers HJ. LTP after stress: up or down? Neural plasticity. 2007;2007.
55. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychological bulletin. 2004;130(3):355-91.
56. Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research: a retrospective 75 years after his landmark brief "letter" to the editor# of nature. Stress (Amsterdam, Netherlands). 2012;15(5):472-8.
57. Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological bulletin. 2007;133(1):25-45.
58. Wallbridge DR, MacIntyre HE, Gray CE, Denvir M, Oldroyd KG, Rae AP, et al. Increase in plasma beta endorphins precedes vasodepressor syncope. Heart. 1994;71(5):446-8.
59. Asakura H, Zwain I, Yen S. Expression of genes encoding corticotropin-releasing factor (CRF), type 1 CRF receptor, and CRF-binding protein and localization of the gene products in the human ovary. The Journal of Clinical Endocrinology & Metabolism. 1997;82(8):2720-5.
60. Muramatsu Y, Sugino N, Suzuki T, Totsune K, Takahashi K, Tashiro A, et al. Urocortin and corticotropin-releasing factor receptor expression in normal cycling human ovaries. The Journal of Clinical Endocrinology & Metabolism. 2001;86(3):1362-9.
61. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertility and sterility. 2005;83(5):1454-60.
62. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Human reproduction (Oxford, England). 2010;25(2):544-51.
63. Yokoyama K, Yamada T, Mitani H, Yamada S, Pu S, Yamanashi T, et al. Relationship between hypothalamic-pituitary-adrenal axis dysregulation and insulin resistance in elderly patients with depression. Psychiatry research. 2015;226(2-3):494-8.
64. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet (London, England). 2011;378(9785):31-40.
65. Mezuk B, Edwards L, Lohman M, Choi M, Lapane K. Depression and frailty in later life: a synthetic review. International journal of geriatric psychiatry. 2012;27(9):879-92.
66. LANDSBERG L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Oxford University Press; 1986.
67. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. Hypertension. 2003;42(4):474-80.
68. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. The Journal of clinical endocrinology and metabolism. 2001;86(2):517-20.
69. Gopal M, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. Sleep medicine. 2002;3(5):401-4.
70. Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2008;93(10):3878-84.
71. Hedner J, Darpo B, Ejnell H, Carlson J, Caidahl K. Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: cardiovascular implications. European Respiratory Journal. 1995;8(2):222-9.
72. Han KS, Kim L, Shim I. Stress and sleep disorder. Experimental neurobiology. 2012;21(4):141-50.
73. Benarroch EE. Basic neurosciences with clinical applications: Elsevier Health Sciences; 2006.
74. Chatterton RT. The role of stress in female reproduction: animal and human considerations. International journal of fertility. 1990;35(1):8-13.
75. Sabban EL, Kvetnansky R. Stress-triggered activation of gene expression in catecholaminergic systems: dynamics of transcriptional events. Trends in neurosciences. 2001;24(2):91-8.
76. Grossman A, Sutton JR. Endorphins: what are they? How are they measured? What is their role in exercise? Medicine and science in sports and exercise. 1985;17(1):74-81.
77. Magiakou MA, Mastorakos G, Webster E, Chrousos GP. The hypothalamic-pituitary-adrenal axis and the female reproductive system. Annals of the New York Academy of Sciences. 1997;816:42-56.
78. Dobson H, Smith RF. What is stress, and how does it affect reproduction? Animal reproduction science. 2000;60-61:743-52.
79. Fox SR, Hoefer MT, Bartke A, Smith MS. Suppression of pulsatile LH secretion, pituitary GnRH receptor content and pituitary responsiveness to GnRH by hyperprolactinemia in the male rat. Neuroendocrinology. 1987;46(4):350-9.
80. Jedema HP, Grace AA. Corticotropin-releasing hormone directly activates noradrenergic neurons of the locus ceruleus recorded in vitro. Journal of Neuroscience. 2004;24(43):9703-13.
81. Bissette G, Klimek V, Pan J, Stockmeier C, Ordway G. Elevated concentrations of CRF in the locus coeruleus of depressed subjects. Neuropsychopharmacology. 2003;28(7):1328.
82. Baum A, Posluszny DM. Health psychology: mapping biobehavioral contributions to health and illness. Annual review of psychology. 1999;50:137-63.
83. Homan G, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Human reproduction update. 2007;13(3):209-23.
84. Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, et al. Physical activity, body mass index, and ovulatory disorder infertility. Epidemiology (Cambridge, Mass). 2002;13(2):184-90.
85. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. Sleep Science (Sao Paulo, Brazil). 2015;8(3):143-52.
86. Shreeve N, Cagampang F, Sadek K, Tolhurst M, Houldey A, Hill CM, et al. Poor sleep in PCOS; is melatonin the culprit? Human reproduction (Oxford, England). 2013;28(5):1348-53.
87. 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(12):725.
88. Zangeneh F, Naghizadeh M, Jafarabadi M. Immune Modulation of Interleukin-1α by Noradrenaline and Cortisol in Women with PCOS (Psychoneuroimmunology Aspect).
89. Hjollund NH, Jensen TK, Bonde JP, Henriksen TB, Andersson AM, Kolstad HA, et al. Distress and reduced fertility: a follow-up study of first-pregnancy planners. Fertil Steril. 1999;72(1):47-53.