Women's Health Bulletin. 2014 Apr; 1(1): e18962. DOI: 10.17795/whb-18962

Published online 2014 April 1. **Research Article**

The Effect of Ramadan Fasting on Hypothalamic Pituitary Ovarian (HPO) Axis in Women with Polycystic Ovary Syndrome

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Received: October 10, 2013; **Revised:** November 23, 2013; **Accepted:** January 5, 2014

Background: Ramadan fasting is a religious practice and an exceptional ritual compared to all other religious conventions. The aim of fasting in Ramadan is to establish a proper religious model of self-control and healthy lifestyle.
Objectives: The purpose of this study was to compare the biochemical neurohormones between women with polycystic ovary syndrome (PCOS) with and without fasting.
Materials and Methods: This study was conducted during July 2011 at the Infertility Center of Royan Institute, and comprised 40 patients diagnosed with PCOS, aged from 20-40 years without any special disease. The study group included 20 women with PCOS and fasting during Ramadan. The control group consisted of 20 non-fasting women with PCOS. The study on the effects of fasting on patients with polycystic ovary syndrome involved demographic data and biochemical stress hormones including cortisol, adrenaline, noradrenaline, beta-endorphin and insulin.
Results: In patients with PCOS, mean of cortisol in subjects with and without fasting were 8.2 ± 4.4 and 11.2 ± 4.7, respectively (P = 0.049). Also the respective median of nor-adrenaline in fasting and non-fasting patients were 1273.5 and 1503.5 (P = 0.047). However, no significant differences were found in adrenalin (P = 0.151), beta-endorphin (P = 0.543) and insulin (P = 0.818) between PCOS two groups.
Conclusions: This study showed that Ramadan fasting is a well known practice to reduce stress hormones in women with PCOS. So, Ramadan, beside its spiritual benefit is a blessing from God for improving human lifestyle.

Keywords: Ramadan fasting; Polycystic ovary syndrome; Stress hormones; Beta-endorphine; Insulin; Sex hormones

1. Background

Islamic fasting is special and novel gift from God Almighty that corrects lifestyle, elevates physical health and boosts spiritual quality of humans. One month fasting in holy Ramadan is a unique annual practice that is beneficial to human health, because studies have shown that brain's biologic clock needs yearly repair (1). According to the holy Quran and prophet's tradition, brain clock must be overhauled in this month, because gates of mercy are open to the faithful and performing this divine duty can coordinate physiologic and psychological organization. Thus fasting adjusts our brain's biologic clock, and the resulting energy switches on human's physical and spiritual lights for eleven months.

1.1. The History of Fasting

The research of anthropologists shows that the primitive tribes used to fast before hunting, harvesting, conducting magical ceremonies or carrying out sacrifices to appease and calm their angry Gods. They usually went on fasting during the spring season for the purpose of having better harvest and fertile soil. The American Indians used to fast to repel the crop's pest and believed that fasting would act as a pesticide. The Mexican Indian along with Peru Incas used fasting as a means of establishing a communion and cordial relationship with their Gods. In ancient Egypt; the Egyptians used to fast before their religious festivals, but it was not compulsory. The Assyrian and Babylonian used to fast for confession of sin and

Implication for health policy/practice/research/medical education:
This study showed that Ramadan fasting can be a good pattern for reducing stress hormones in PCOS women and so sympathetic nervous system may offer a new therapeutic target for this syndrome.

God's forgiveness. Among the supporters of oriental religions, Hindus, the followers of Confucius and specifically the Buddhist and people of Tibet observed fasting. In various religions the quality, duration and adopted rules or regulation for fasting was different (2). Based on follower of the Abrahamic faith; fasting was a compelling need for all God's religions, as it was clearly emphasized Baqara verse 183 of holy Quran. The Christian famous feast is the day of Easter; Christians do fast in order to cleanse their spirit and practice strict self-denial. In Judaism; fasting is the real way to get closer to God, Fasting for Jews means complete abstaining from food and drink. Traditionally observant Jews fast six days of the year. Yom Kippur is considered to be the most important day of the Jewish year and fasting as a means of repentance is expected of every Jewish man or woman above the age of bar mitzvah and bat mitzvah respectively. It is so important to fast on this day, that only those such as the ill or frail who are at risk for mortal danger by fasting are exempt, because endangering a life is against a core principle of Judaism (3). Fasting in the history of anthropology indicates the truth; that even in the past, primitive tribes also sought the consent of their gods and asked for their help in times of needs. Ramadan is the holy month for Islamic World, where, food and fluid consumption is restricted to the pre-sunrise and post-sunset hours. It is obligatory for all healthy adult Muslims to abstain from eating, drinking, and smoking each day from dawn to sunset during this month (4).

1.2. The Historical Aspects of Fasting and its Effect on PCOS

The sixth year of Hegira marks the first time in Islam that fasting was recognized and practiced. After the peace of Hodaybieh, Prophet Mohammad migrated to Medina city, where he practiced fasting in the holy month of Ramadan. In Islam fasting possesses a very special place. In this context, Quran states: "The faithful does understand that fasting is a necessity for you all, as it had been before you" (Baqara/183 verse). According to this verse, it is very clear that fasting had existed in all religions. God for the purpose of clarity as stated in Quran, with an example which reflects on the birth of Christ, and addressed Madonna by saying "if you see others tell them to fast for me. This holy verse indicates the special Grace of God for fasting to the faithful. In the history of religions before and after the Islam, fasting in the Islamic nations has been a necessity. Prophet Mohammad (PBUH) stipulated that everything humans do is only for their own, except fasting which is considered for me and rewarded without any mediators (5). This order of prophet stresses the great importance of holy month of Ramadan which is God's banquet and as Prophet Mohammad had mentioned it is the God's holy reception for all Muslims. There are many reports about the benefits of Ramadan fasting on physical health, but to our knowledge there is no report on the effect of Ramadan fasting on polycystic ovarian disease.

Polycystic ovary syndrome (PCOS) is a complex, multifaceted, heterogeneous disorder, affecting 4% to 18% of women in reproductive age and is associated with reproductive, metabolic and psychological dysfunction (6). Its prevalence among infertile women is 15% -20% (7). Although menstrual irregularities in adolescent girls are often attributed to an immature Hypothalamus-Pituitary-Gonadal (HPG) axis (8), many adolescents with persistent menstrual abnormalities may feel apprehensive about PCOS. Women with ovulatory menstrual cycles have a circadian rhythm superimposed on the menstrual-associated rhythm; in turn, menstrual events affect the circadian rhythm. The investigations into the biological consequences of circadian disruption in women will offer insight into some menstrual-associated disorders, including mood changes, as well as reproductive function and possible links with breast cancer (9). Many of the common features of PCOS, such as central obesity, hyperinsulinaemia and obstructive sleep apnoea, are associated with chronic sympathetic overactivity. This is suggestive of possible involvement of sympathoexcitation in the pathogenesis of this condition (10). The clinical features include reproductive manifestations such as reduced frequency of ovulation and irregular menstrual cycles, reduced fertility, polycystic ovaries on ultrasound, and high male hormones such as testosterone which can cause excess facial or body hair growth and acne. Previous studies have shown that PCOS may cause some psychological disorders. The relationships between the psychological health aspects and the clinical characteristics of PCOS are not yet clear. PCOS affects quality of life and can worsen anxiety and depression either due to the features of PCOS or due to the diagnosis of a chronic disease (11). The results confirm Adali´s and Hirschberg´s findings (12), suggesting that treatment of PCOS should tackle both physical and psychological complaints. This is because psychological distress reduces amenable motivation, which is the key to complying with treatment and dietary management of PCOS (13). Studies in recent decades show that lifestyle intervention improves body composition and Ramadan fasting can be a good pattern for Muslims to improve their morals and habits which they believe to be beneficial. The purpose of the present study was to investigate the possible effect of these changes on the circadian rhythm of cortisol, cathecolamines and sex hormones in PCOS women.

2. Objectives

The purpose of this study was to compare the biochemical neurohormones between polycystic ovary syndrome (PCOS) women with and without fasting.

3. Materials and Methods

This study was performed in Infertility Center of Royan Institute in July 2011, coinciding with month of Ramadan. The study comprised 40 patients diagnosed with PCOS according to the criteria of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine (ESHRE/ASRM) (14).

The study group included 20 women with PCOS who were fasting during Ramadan, and the control group consisted of 20 PCOS women without fasting. The effect of Ramadan fasting was evaluated with respect to stress neurohormones, serum cortisol, Adrenaline (A), Noradrenalin (NA) and Beta-endorphin (B-end), Insulin as well as sex hormones such as FSH, LH, Testosterone. The participants aged 20-40 years and except having PCOS they lacked no apparent illness. BMI was calculated as weight (kg)/height 2 (m) and was below 28. This study was approved by ethics committee of Tehran University of Medical Sciences. Blood sample was obtained from all participants before 8 AM. All specimens were kept at -80 C° until used. The samples were measured by relevant ELISA kits. Clinical data including information about hirsutism, acne, menstrual cycle as well as situation of fasting such as nutrition and sleep was gathered by physical examination and interview. The Elisa kits were used to measure the serum levels of Adrenaline, Nor-adrenaline (Oxidized LDL Elisa), Beta-endorphin and estradiol (β-EP ELISA Kit from China), Cortisol and Insulin (ELISA kit, Diametra from Italy), FSH, LH and testosterone (ELISA kit, Monobind from USA) at the Laboratory of Pathology of Royan. Clinical and anthropometric variables, including body mass index (BMI) calculated as weight kg/height (m) 2, and demographic social questionnaires were used for data collection. This questionnaire comprised age, education, occupation, and duration of illness.

1.3. Statistical Analysis

Data are presented as Mean ± Standard Deviation and Median. Comparison of symptoms between study groups was done using Chi square test. Kolmogorov-Smirnov test was used to check normality of distribution. FSH, LH, Testosterone, Insulin and Cortisol had normal distribution and were compared between two groups by t test. Mann-Whitney test was used for comparing the other hormones that did not follow normal distribution. Spearman rank correlation coefficient was used to assess relationship between the hormones. Statistical analysis was done using SPSS 18 (SPSS Inc, Chicago, Ill), and p value less than 0.05 were considered significant.

4. Results

This study included 40 women with PCOS of which 20 were in fasting (case) and 20 in non-fasting groups (control). Mean age of fasting group was 29.4 ± 4.60 and in non-fasting group it was 28.8 ± 3.67 years (P = 0.658). The mean weight in fasting group was 63.9 ± 5.78 Kg and in non-fasting was 66.3 ± 6.42kg (P = 0.221). Acne was found in 6 (30%) women in fasting and 5 (25%) in non-fasting women. Acne (P = 0.723), hirsutism (P = 0.451), and irregular menstrual period (P = 0.231) were the same in both groups. Demographic and symptoms in participants are presented in Table 1.

The results of biochemical tests measuring FSH (P = 0.542), LH (P = 0.827) and testosterone (P = 0.683) were not significantly different between the two groups (Table 2). The mean cortisol hormone significantly decreased in fasting group (8.2 ± 6.7, P = 0.049) as compared to 11.2 ± 9.3 in non-fasting women.

Nor-adrenaline decreased in fasting group (1176 ± 439, P = 0.047), compared to 1430 ± 404 in non-fasting subjects. There was no significant changes in adrenalin level between fasting and non-fasting groups (P = 0.151. There were no significant differences in beta-endorphin (P = 0.543) and insulin (P = 0.818) levels between the two groups (Table 3). Spearman rank correlation coefficient showed an inverse correlation between insulin and noradrenalin (r = -0.328, P = 0.039). However, no significant inverse correlation was observed between beta endorphin, adrenalin (P = 0.256). Also there was no significant direct correlation (P = 0.224) between adrenalin (P = 0.464), and noradrenalin (Table 4).

Table 1. Demographic Information and Symptoms of Women with PCOS

Variables, Mean ± SD	Not Fasting, (N = 20)	Fasting, (N = 20)	P Value
Age, year	28.80 ± 3.86	29.40 ± 4.60	0.65
Age at marriage time, year	21.00 ± 3.09	21.15 ± 3.91	0.89
Infertility duration, year	7.55 ± 4.05	6.60 ± 3.73	0.44
Weight, kg	66.30 ± 6.42	63.90 ± 5.78	0.22
Variables, No. (%)	Count (%)	Count (%)	
Acne	5 (25)	6 (30)	0.72
Hirsutism	17 (85)	14 (70)	0.45
Irregular menstrual cycle	20 (100)	17 (85)	0.23

Table 2. Biochemical Tests of PCOS Women in Ramadan Fasting

	Control, (N = 20)		Ramadan Fasting, (N = 20)		P Value
	Mean ± SD	Median	Mean ± SD	Median	
FSH (mIU/ml)	5.60 ± 1.96	5.55	5.24 ± 1.72	5.40	0.54
LH (mIU/ml)	8.08 ± 6.77	5.45	8.51 ± 5.46	7.10	0.83
Testosterone (ng/ml)	1.73 ± 1.18	1.45	1.94 ± 1.97	1.20	0.68
Cortisol (μg/dL)	11.2 ± 4.7	9.3	8.2 ± 4.4	6.7	0.04

Table 3. Hormonal Tests of PCOS Women in Ramadan Fasting

Hormones	Control, (N = 20)		Ramadan Fasting, (N = 20)		P Value
	Mean ± SD	Median	Mean ± SD	Median	
Adrenaline, (pg/ml)	135.49 ± 97.90	110.00	98.83 ± 82.96	84.00	0.15
Nor-adrenaline, (pg/ml)	1430.30 ± 404.46	1503.50	1176.15 ± 439.16	1273.50	0.04
Beta endorphin, (ng/Lit)	233.2 ± 494.6	47.7	360.2 ± 759.2	55.6	0.54
Insulin, (mIU/Lit)	19.2 ± 18.2	11.5	19.7 ± 20.8	11.5	0.82

Table 4. Spearman's Correlation Coefficient between Hormones in PCOS Women in Ramadan Fasting

	Cortisol	Adrenaline	Nor-adrenaline	Beta endorphin	Insulin
Cortisol					
Correlation		0.043	0.170	-0.030	-0.140
P Value		0.793	0.294	0.856	0.390
Adrenaline					
Correlation	0.043		0.197	-0.184	-0.057
P Value	0.793		0.224	0.256	0.726
Nor-adrenaline					
Correlation	0.170	0.197		-0.119	-0.328
P Value	0.294	0.224		0.464	0.039
Beta-endorphin					
Correlation	-0.030	-0.184	-0.119		0.142
P Value	0.856	0.256	0.464		0.384
Insulin					
Correlation	-0.140	-0.057	-0.328	0.142	
P Value	0.390	0.726	0.039	0.384	

5. Discussion

Polycystic ovary syndrome (PCOS) is a common endocrine condition associated with long-term health risks, including type 2 diabetes and vascular dysfunction in addition to reproductive sequelae. Many of the common features of PCOS, such as central obesity, hyperinsulinaemia and obstructive sleep apnea (OSA), are associated with chronic sympathetic overactivity, suggesting that sympathoexcitation may be involved in the pathogenesis of this condition. The aim of this study was to investigate the effect of Ramadan fasting on the sympathetic nervous system activity expressed as stress hormones in women with PCOS. The recent studies on patients with PCOS showed evidence of increased muscle sympathetic nerve activity (MSNA). This affected heart rate variability and delayed post exercise heart rate recovery, compared with age and BMI-matched controls, suggesting a generalized increase in sympathetic nerve activity (10). The increased secretion of noradrenalin hormone, a stress-related chemical, occurs in response to excessive levels of insulin, and under conditions of emotional upset and glucocorticoids such as cortisol is also a stress-associated chemical in women. The female reproductive system is regulated by the hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-ovarian (HPO) axes. The

principal regulators of HPO axis are HPA and gonadotropin-releasing hormone (GnRH) that stimulates FSH and LH secretion with subsequent release of estradiol

andprogesterone by the ovary (15). Hypothalamic target neurons of estrogen include neurosecretory neurons (GnRH), dopamine neurons, and local circuitry neurons like proopiomelanocortin (POMC) and γ-aminobutyric acid (GABA) neurons. These and other hypothalamic neurons are involved in regulating numerous homeostatic functions comprising reproduction, thermoregulation, stress responses, and feeding and motivated behaviors (16). The HPA axis, when activated by stress, exerts an inhibitory effect on the female reproductive system, corticotropine releasing hormone (CRH) and CRH-induced proopiomelanocortin peptides, such as β-endorphin, inhibit hypothalamic GnRH secretion (17). In addition, glucocorticoids suppress gonadal axis function at the hypothalamic, pituitary and uterine level (18). Glucocorticoid administration significantly reduces the peak luteinizing hormone response to intravenous GnRH, suggesting an inhibitory effect of glucocorticoids on the pituitary gonadotroph (19). The locus coeruleus (LC) provides the sole source of noradrenaline (NA) and increasing tonic discharge of LC neurons elevates extracellular levels of NA in the cortex and thalamus. The LC-NA system has been shown to be activated by a myriad of stressors and opioids are important mediators of the LC-NA system during stress (20). The LC is densely innervated by processes exhibiting endogenous opioid peptides (Figure 1) (21). Endogenous opioids have modulating role on cathecolamine secretion, and studies of these effect show that, opioids inhibit the release of cathecolamine during stress (21, 22). These studies show that there is interaction between sympathetic and opioid systems in HPO, in modeling of PCOS in rat, as reported by Zangeneh et al., in 2011 (23).

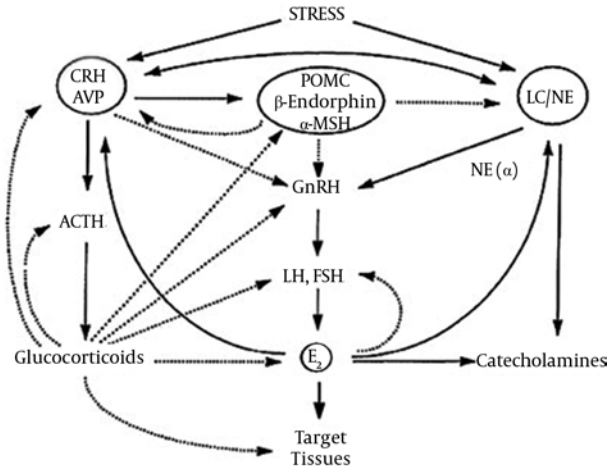

Figure 1. Heuristic representation of the interplay among the hypothalamic-pituitary-adrenal axis, the locus ceruleus/norepinephrine (LC/NE) sympathetic system and the hypothalamic-pituitary-gonadal axis. The dotted lines represent inhibition while the solid lines represent stimulation (24).

Peripherally, the analyzed relationship between sympathetic and opioid system in pathogenesis of stress demonstrates a protective role by the peripheral mu-opioid receptors associated with decrease in activity of sympathico-adrenal system. This phenomena in the heart leads to an increase in stress-related heart damage via increasing sympathical influence on the myocardium (25) and now the question is, how does this pathogenetic process affects reproductive system?

In this study, our data showed that Ramadan fasting reduces the level of serum cortisol and noradrenaline (stress hormones) in study group (PCOS). But adrenaline decreasing and beta-endorphin increasing were not significant. Endogenous opioids have a tonic inhibitory effect on sympathetic tone, (26) and the subsequent increase in beta-endorphin reduces the amount of catecholamines in women with PCOS. According to our study, reduced noradrenaline in both subjects indicated reduced stress in patients in Ramadan and unchanged levels of sex hormones. Marshal's study in 2001 showed catecholamines stimulate GnRH release, whereas endogenous opioid peptides and prolactin inhibit GnRH secretion (27). Thus, the unaltered levels of sex hormones observed in our study could be due to reduced noradrenaline and increased beta-endorphin. Lack of change in serum insulin levels could also represent reduction in noradrenaline. The general action of sympathetic nervous system is to mobilize the body's nervous system fight-or-flight response, a command issued by the hypothalamus. This system in brain serves globally as an alarm system that decreases neurovegetative functions, such as eating and sleeping, and contributes to accompanying increases in autonomic and neuroendocrine responses to stress, including HPA axis activation (28). Reciprocal connections exist between the CRH and LC/NE system neurons of the central stress system, with mutual stimulation of CRH and norepinephrine, the latter being primarily through noradrenergic receptors (28, 29). These results indicate that chronic sympathetic overactivity in PCOS can be reduced by fasting. Fasting can reduce stress neurohormone levels and to insure the physical and mental health. On the other hand, the sympathetic nervous system may thus offer a new therapeutic target in PCOS. However, more extensive and longer-term studies are needed before these treatments can be applied to clinical practice. Finally, it should be noted that the time limit during Ramadan is the main reason for low sample size in this study therefore; more samples are needed for a significant response. This study showed that Ramadan fasting can be a good pattern for reducing stress hormones in PCOS women and so sympathetic nervous system may offer a new therapeutic target for this syndrome.

Acknowledgements

This study was conducted in the Infertility Center of

Royan Institute. We thank Royan's Research Council and Mrs. Rastegar helped us in carrying out this study.

Financial Disclosure

The authors would like to thank the Iran University of Medical Science for funding this study.

Funding/Support

This work was supported by the Research Institute for Islamic and Complementary Medicine (RICM), Iran University of Medical Sciences, Tehran, Iran.

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