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Comparison of Metabolic and Hormonal Profiles of Women With and Without Premenstrual Syndrome: A Community Based Cross-Sectional Study

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Abstract

Background: Premenstrual syndrome (PMS) is reported by up to 85% of women of reproductive age. Although several studies have focused on the hormone and lipid profiles of females with PMS, the results are controversial.
Objectives: This study was designed to investigate the association of hormonal and metabolic factors with PMS among Iranian women of reproductive age.
Materials and Methods: This study was a community based cross-sectional study. Anthropometric measurements, biochemical parameters, and metabolic disorders were compared between 354 women with PMS and 302 healthy controls selected from among 1126 women of reproductive age who participated in the Iranian PCOS prevalence study. P values < 0.05 were considered significant.
Results: Prolactin (PRL) and triglycerides (TG) were significantly elevated in women with PMS, whereas their testosterone (TES), high density lipoprotein (HDL) and 17-hydroxyprogesterone (17-OHP) levels were significantly less than they were in women without the syndrome (P < 0.05). After adjusting for age and body mass index (BMI), linear regression analysis demonstrated that for every one unit increase in PMS score there was 12% rise in the probability of having metabolic syndrome (P = 0.033).
Conclusions: There was a significant association between PMS scores and the prevalence of metabolic syndrome. Further studies are needed to confirm and validate the relationships between lipid profile abnormalities and metabolic disorders with PMS.

Keywords: Metabolic Syndrome, Premenstrual Syndrome, Testosterone, Hypertension, Prolactin

1. Background

Premenstrual syndrome (PMS) is a set of somatic and psychological symptoms which occur during the luteal phase of the menstrual cycle (1). Up to 85% of women of reproductive age report experiencing one or more of the symptoms of PMS (2) and approximately 5% suffer from a severe form of PMS called premenstrual dysphoric disorder (PMDD) (3).

The exact cause of PMS still remains unclear and many factors are supposed to contribute to the condition; therefore, it has been proposed that PMS is a multicausal problem (4). According to the neurobiological data on the subject, the activities of the neurotransmitter system are mainly affected by gonadal steroids. Through this process, estrogens, progestins, and androgens may be indirectly implicit in the development of depression (5, 6).

Although several studies have focused on the hormone and lipid profiles of women with PMS, they report findings that are controversial. For example, several studies that have assessed the connection between PMS and testosterone levels, present findings that conflict (7, 8). Similarly, there is also disagreement over the association between prolactin (PRL) levels and PMS; while Benedek-Jaszmann and Hearn-Sturtevant reported higher levels of PRL in women with PMS (9), Backstrom and Aakvaag failed to find any association (10). There are also conflicting data on the mean concentration of cholesterol among women with and without PMS (11). By conducting epidemiological and clinical studies, many researchers have uncovered conflicting results regarding the association between estradiol (E2), follicle-stimulating hormone (FSH), testosterone (T), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) levels and depression (12-15).

To date, few studies have evaluated the association be-

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tween hormonal and metabolic factors and PMS. Most of the results were restricted by their small sample size, inappropriate inclusion criteria for women with PMS, and by their comparison of a limited number of variables between the two groups of women, both with and without PMS (10, 16). Hence, it seems to be necessary to conduct a comprehensive community based study.

2. Objectives

As a result, in the present study we aimed to investigate the association of hormonal and metabolic factors with PMS among Iranian women of reproductive age.

3. Materials and Methods

3.1. Subjects

The subjects of this study were selected from among the participants in the Iranian PCOS prevalence study which was a community based cross-sectional study of 1026 women, aged 18 - 45 years, conducted between 2009 - 2010 (17). The eligible women were invited to participate in a comprehensive interview and their blood pressure, anthropometric, hormonal, and metabolic measurements were documented.

Data were completed for all but 97 women who did not come to the clinics and 19 participants whose hormonal and metabolic profiles were unavailable. We also excluded women who were using antidepressants (n = 34), oral contraceptive pills (n = 151), or taking hormonal medication for irregular menses. Furthermore, those women who were pregnant at the time of the study (n = 43) and menopausal women (n = 37) were also excluded. Finally, after the exclusion of the women who did not meet our inclusion criteria, 656 women were enrolled in the study.

The American college of obstetricians and gynecologists' (ACOG) criteria were used to diagnose PMS. According to these criteria, the women needed to experience at least one of each of the following affective symptoms (depression, angry outbursts, irritability, anxiety, confusion, social withdrawal) and one somatic symptom (breast tenderness, abdominal bloating, headache, swelling of extremities) during the five days before menses in order to be diagnosed as having PMS. Each symptom must appear in three consecutive menstrual cycles and be scored on a scale of 1 (low intensity), 2 (moderate intensity) and 3 (severe intensity). The sum of the PMS score ranges from 2 to 30. Using these criteria, our study participants were categorized into two groups: women with PMS (n = 354) and those without PMS (n = 302).

All the participants underwent clinical examinations, where their body weight, height, waist and hip circumferences, and blood pressure were measured by trained staff. Height and weight were also measured with the subjects wearing light clothes but without shoes, using standard apparatus.

Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height and waist circumferences (WC) were measured to the nearest 0.5 cm using a measuring tape. The waist was measured midway between the lower rib margin and the iliac crest, after a gentle expiration. Body mass index (BMI) was calculated by dividing a participant's weight in kilograms by their height in meters squared (kg/m^2). A blood sample that was used to determine biochemical measurements was taken from each subject on the second or third day of their menstrual cycle, after 12 hours of overnight fasting. Blood samples were collected in EDTA treated test tubes. Written informed consent was obtained from all participants before study entry.

3.2. Laboratory Measurements

17-hydroxyprogesterone (17OH-P), total testosterone (TT) and androstenedione (A4) were measured by enzyme immunoassay (EIA), (Diagnostics Biochem Canada Inc., Ontario, Canada). Sex hormone-binding globulin (SHBG) was measured by immunoenzymometric assay (IEMA), (Mercodia, Uppsala, Sweden). All ELISA tests were performed using a Sunrise ELISA reader (Tecan Co., Salzburg, Austria).

Luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), and thyroid stimulating hormone (TSH) were measured by immunoradiometric assay (IRMA) (Izotop, Budapest, Hungary) using a gamma counter (Wallac Wizard, Turku, Finland).

It has been shown that in women, the free androgen index (FAI) has a good correlation with free testosterone measured by a physical separation method (18); therefore, in this study the FAI was calculated by using the formula:

$$\mathrm{FAI} = \frac{\mathrm{TT(nmol/}L)}{\mathrm{SHBG(nmol/L)}} \times 100 \quad (1)$$

The intra- and inter-assay coefficients of variation for TT were 5.6% and 6.6%; for SHBG, 1.2% and 5.7%; for A4, 2.2% and 3.5%; for LH, 3% and 5.8%; for FSH, 3.5% and 4%; for TSH, 1.7% and 3.4%, and for PRL, they were 2.1% and 4.1%, respectively.

3.3. Definition

According to the ACOG practice guidelines for the diagnosis of PMS, one or more of the disturbing affective or somatic symptoms must have occurred in the five days

before menses in each of three previous menstrual cycles. Metabolic syndrome, based on the joint interim statement (JIS) definition, was considered to be the presence of any three of the following five risk factors (19): WC $\geq$ 95 (country-specific cutoff point for Iranians (20), HDL < 50, SBP $\geq$ 130 or DBP $\geq$ 85, TG $\geq$ 150 and FBS $\geq$ 100.

According to the sixth report of the joint national committee (JNC-VI) criteria, hypertension or high BP was defined as mean SBP _140 mmHg, mean DBP _90 mmHg, or applied to a person undergoing current treatment for hypertension with prescription medication (21). Based on the American diabetes association's (ADA) definition of diabetes, participants who met the following criteria were considered to be diabetic: 1) using anti-diabetic drugs or with fasting blood sugar (FBS) of _7 mmol/L or 2-h plasma glucose (2hPG) _11.1 mmol/L; 2) those with 2hPG between 7.77 and 11.1 mmol/L were defined as IGT, and; 3) FBS between 5.6 - 6.9 mmol/L was defined as impaired fasting plasma glucose (IFG) (10, 22). Based on ATP II, dyslipidemia was defined as TC _240 mg/dL or LDL _160 mg/dL or TG _200 mg/dL or HDL < 35 mg/dL (23).

Biochemical hyperandrogenism was detected by FAI and/or A4 levels above the upper 95th percentile for the 362 women studied who were not on any hormonal medication and had no clinical evidence of hyperandrogenism, ANOVU, or PCO. Specifically, the upper normal limits for total T were = 0.88 ng/mL, A4 = 2.3 ng/mL, and FAI = 5.47.

3.4. Statistical Analysis

Continuous variables were checked for normality using the one-sample Kolmogorov-Smirnov test, and expressed as mean, standard deviation, and/or median (IQ: 25 - 75), as appropriate. Correlations between hormone concentrations and premenstrual syndrome scores were checked using the Pearson correlation. Linear regression (forward method) was used to identify the association between PMS scores and metabolic disorders (dependent variable) after adjustment for age and BMI. The data analysis was performed using the SPSS 15.0 PC package (SPSS Inc., Chicago, IL).

4. Results

The demographic characteristics of the women who did not complete the questionnaire or those without hormonal measurements available did not significantly differ from those who completed the study procedure (data has not been presented). The mean age of the participants was 32.9 years. Approximately 75% of them were married and 72% were housewives. According to our findings, the education levels in women with PMS were significantly higher than those without the condition. However, there was no significant association between PMS and other demographic characteristics. Table 1 demonstrates some of the demographic, reproductive, and anthropometric characteristics of the studied women, as divided into two groups, i.e. women with PMS and those without it.

Table 2 shows a comparison of the hormonal, metabolic, and lipid profiles of women with and without PMS. Our results suggest that there was a significant increase in PRL and TG among women with PMS, whereas TES, HDL and 17OH-P were significantly decreased when compared to women without PMS. Mean PRL and TES for women with PMS were 18.5 and 0.58, respectively, whereas for the controls these values were 16.3 and 0.67, respectively (P < 0.05). The mean serum levels of TG, HDL and 17OH-P for women with and without PMS were 147.3, 44.2, and 1.8 versus 128.2, 46.3, and 2, respectively. Using ANCOVA, we compared all the above variables between the two groups in order to adjust for age and BMI; the results of the t-test analysis were not significantly different.

The results of the Pearson correlation analysis showed that T4, PRL, TES, and 17OH-P had significant correlations with PMS scores among the affected women (P < 0.05). Other variants, including serum levels of TSH, LH, SHBG, HDL, TG, insulin, FBS, LDL, CHL, systolic BP, diastolic BP, LH/FSH, FAI, and A4 were not significantly correlated with PMS. After adjusting for age and BMI, using partial correlation the results remained unchanged.

After adjusting for age and BMI, a linear regression analysis demonstrated a significant association between PMS scores and the prevalence of metabolic syndrome (P = 0.033). According to our findings, for every one unit increase in PMS score there was a 12% increase in the probability of having metabolic syndrome. Using a linear regression analysis we found a non-significant association between PMS scores and other metabolic disorders, such as diabetes, hyperandrogenism, dyslipidemia, hypertension, and hypothyroidism (Table 3).

5. Discussion

In the present study, we assessed a wide range of hormones and metabolites in order to establish their associations with PMS. The association found between lower TT levels and PMS in the present study contradicts the findings of Bloch et al.'s study (7) which indicated significantly lower TT and free T levels in women with PMS. However, Eriksson et al. (16) and Backstrom and Aakvaag (10) discussed the contrary. It has been found that low testosterone in women can cause a number of physical and emotional symptoms, including depression, loss of sexual desire, and declining libido (24-26). Despite there being a

Table 1. Demographic, Reproductive, and Anthropometric Characteristics of Women With and Without Premenstrual Syndrome

Variables	Premenstrual Syndrome[a]		P Value[b]
	Positive	Negative	
Age, y	34.2 ± 7.5	33.8 ± 7.7	0.58
Education, y	9.5 ± 4.2	8.3 ± 4.6	0.003
Marriage age, y	20.0 ± 3.3	8.3 ± 4.6	0.51
Number of pregnancies	2.7 ± 1.4	1.9 ± 3.2	0.75
Number of parity	2.4 ± 1.3	2.8 ± 1.6	0.86
Number of abortions	0.33 ± 0.5	0.34 ± 0.89	0.86
Menstrual intervals, d	29.0 ± 11.9	28.4 ± 4.3	0.53
Body mass index, kg/m^2	27.8 ± 5.4	26.7 ± 4.9	0.01
Waist circumference, cm	85.9 ± 12.2	84.9 ± 12.01	0.3
Systolic BP, mmHg	108.1 ± 14.2	108.8 ± 12.6	0.46
Diastolic BP, mmHg	69.1 ± 11.2	69.3 ± 10.3	0.72
Income status, Rials			0.06
More than 3000000	69	66.2	
Less than 3000000	31	33.8	
Marital status			0.51
Married	92.5	82.1	
Never married	7.5	17.9	
Job status			0.25
Housewife	72	76.7	
Employed	28	23.3	

[a] The values are expressed as mean ± SD except income, marital and job statuses that are presented as %.
[b] Comparison carried out using t-tests or χ^2 tests for continuous and categorical variables, respectively. P values of less than 0.05 were considered statistically significant in both tests.

limited number of studies concerning the effects of testosterone on mood, the results show that testosterone treatment per se, or with estrogen, improves mood in women (27).

We observed significantly lower 17-OHP levels among women with PMS which are findings that contradict those of Eriksson et al. (16) who assessed women with PMS during the luteal phase and reported higher 17-OHP levels when compared to age-matched controls; these differences may be explained by the difference in the age of the subjects and the effects of age on hormone levels.

The present study demonstrated that the serum PRL level is significantly higher in women with PMS, which is a finding that is in line with previous studies (9, 28). By contrast, another study (10) reported that the mean plasma prolactin level among 15 women affected with PMS was not significantly different from that of the 17 women in the control group; it appears that because of the small sample size, the researchers found no association between PRL and PMS. Prolactin plays an indirect role in premenstrual syndrome and may cause renal retention of water, sodium, and potassium, and it interacts with lithium. Prolactin can also interact with ovarian hormones to cause symptoms of depression, anxiety, or irritable hostility (29).

The data report higher levels of total cholesterol in women with PMS with no significant alteration in TG and HDL (11); conversely, our data showed higher TG and lower HDL levels. In addition, we uncovered a significant association between PMS scores and metabolic syndrome. To our knowledge, this is the first study examining the association of metabolic disorders in Iranian women with PMS. Several studies have demonstrated that depression is significantly associated with metabolic syndrome; for example, Raikkonen et al. (8) demonstrated that psychosocial factors predict the risk of developing metabolic syndrome. Interestingly, Skilton et al. (30) also suggest that there is an association between metabolic syndrome and higher rates of depression. Since depression is one of the main crite-

Table 2. Comparison of Hormonal, Metabolic, and Lipid Profiles Between Women With and Without Premenstrual Syndrome

Variables	Premenstrual Syndrome[a]		P Value[b]
	Positive (n = 354)	Negative (n = 302)	
Thyroid stimulating hormone, mIU/L	3.4 ± 2.8	3.4 ± 3.3	0.72
Thyroxine, μg/dL	8.0 ± 1.8	8.1 ± 2.0	0.59
Prolactin, ng/mL	18.5 ± 14.1	16.3 ± 12.4	0.03
Luteinizing hormone, mIU/mL	5.2 ± 3.6	5.5 ± 5.0	0.47
Follicle stimulating hormone, mIU/mL	7.7 ± 6.1	7.5 ± 5.6	0.75
Luteinizing hormone/follicle stimulating hormone ratio	0.83 ± 0.7	1.14 ± 5.7	0.29
Total testosterone, ng/mL	0.58 ± 0.29	0.67 ± 0.4	0.002
17-hydroxyprogesterone, ng/mL	1.8 ± 1.0	2.0 ± 1.2	0.04
Free androgen index	3.5 ± 2.5	3.9 ± 2.8	0.07
Androstenedione, ng/mL	1.5 ± 0.60	1.6 ± 0.6	0.13
Sex hormone binding globulin, μg/dL	66.4 ± 25.1	67.2 ± 24.3	0.66
Insulin, μU/mL	8.5 ± 6.3	8.2 ± 6.8	0.56
Homeostasis model assessment-insulin resistance, mol × μU/L^2	2.1 ± 2.02	2.03 ± 2.9	0.7
Fasting blood sugar, mg/dL	88.3 ± 20.4	88.1 ± 24	0.90
Triglycerides, mg/dL	147.3 ± 99.6	128.2 ± 77.9	0.006
Low-density lipoprotein, mg/dL	109.7 ± 34.5	106.8 ± 31.2	0.25
Cholesterol, mg/dL	183.4 ± 40.2	178.8 ± 36.4	0.12
High-density lipoprotein, mg/dL	44.2 ± 12.9	46.3 ± 13.4	0.04

[a] The values are expressed as mean ± SD.
[b] Comparison between means was made using a t-test. P values < 0.05 were considered statistically significant.

Table 3. Summary of the Linear Regression Analysis for Variables Predicting Premenstrual Syndrome[za,b]

Variables	Beta Coefficients	95% CI for Beta	P Value
Total score of PMS	0.123	0.099 - 0.211	0.033
BMI (kg/m^2)	0.087	0.064 - 0.197	0.014
Age, y	0.033	0.010 - 0.051	0.043

Abbreviations: BMI, body mass index; CI, confidence interval; PMS, premenstrual syndrome.
[a] R^2 = 0.002 and adjusted R^2 = -0.001.

ria of diagnosing PMS, it can be speculated that PMS and metabolic syndrome are associated.

According to the data produced by this study, there was no significant association between insulin levels and PMS, which is a consonant result with that of Zarei et al. (31). Eriksson et al. (16) found no significant difference between PMS cases and controls in SHBG levels, which was also consistent with our findings.

One of the strengths of our study was the large cross-sectional community based sample that it used. Since most similar studies have focused on the small number of variants that contribute to PMS disorders, we were able to investigate a broad range of anthropometric parameters and hormone levels in order to determine the independent association between endogenous hormones and metabolic parameters in multivariate analyses. However, a potential limitation that must be recognized is that we used HOMA-IR as a surrogate marker for assessing insulin resistance (IR); in spite of the good correlation between HOMA-IR and gold standard clamp methods, it might be inaccurate in women with PCOS. Moreover, we did not measure free testosterone due to our inability to access a proper method for its measurement. However, we calculated the FAI using Equation 1 it has been shown that FAI

correlates with free testosterone as measured by the physical separation method in women, which is the same as calculated free testosterone (17).

In conclusion, we found a significant association between PMS scores and the prevalence of metabolic syndrome. Moreover, we observed higher levels of PRL and lower levels of TES, OHP-17, TG, and HDL among women with PMS, when compared to women without the syndrome. Further studies are needed to confirm and validate the relationships between lipid profile abnormalities and metabolic disorders with PMS.

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Footnotes

Authors' Contribution: Somayeh Hashemi and Fahimeh Ramezani Tehrani participated in the study design, data analysis, and drafting of this manuscript. Similarly, Nader Mohammadi and Marzieh Rostami Dovom helped with the data collection, data analysis, and drafting of the manuscript. Masumeh Simbar and Fereidoun Azizi contributed to the study design and drafting of the manuscript.

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