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Treatment of Premenstrual Syndrome with Progesterone in Women with Polycystic Ovary Syndrome

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Abstract

Introduction: Premenstrual Syndrome (PMS) is defined as a group of disorders characterized by emotional and physical symptoms that occur in the luteal phase of the menstrual cycle and subside following menstruation. The reported prevalence of severe PMS is variable between 3% and 24%. Etiology of PMS remains unknown but cyclical ovarian activity and the effect of estradiol and progesterone on the neurotransmitters serotonin and gamma-aminobutyric acid appear to be key factors. One hypothesis that the cause of PMS is the deficiency of progesterone and its derivatives. Polycystic Ovary Syndrome (PCOS) is characterized with chronic anovulation and oligo-ovulation. Due to this there is a distinct deficiency of progesterone and its derivatives in PCOS. The aim of this study was to investigate the efficiency of progesterone therapy for PMS in woman with PCOS.

Materials and methods A randomized double blind controlled trial was performed on 60 women with PCOS and PMS. In the study group (progesteron group = group A, n=30), progesteron in a total amount of 300 mg was prescribed for a per day basis on three times a day, and in the control group (placebo group=group B, n=30) placebo capsules, which were completely similar to progesteron capsules were prescribed from day 15 to day 25. The severity and duration of symptoms were compared in both groups before treatment and 3 months after the beginning of treatment with Visual Analog Scala (VAS). Participants were requested to answer questions about their recurrent experience of 16 symptoms during the premenstrual phase. Data were analyzed using the Statistical Package for Social Science (SPSS, version 15.0).

Results: We investigated 60 females (mean age progesterone group / placebo group= 26.6 ± 2,5/ 27 ± 1,8years; range = 18-35 years). Two or more premenstrual symptoms were detected in 95.5% of the participants. The most frequent symptoms are depression, anxiety, abdominal bloating, mood swings, breast tenderness. Statistical significant decline was seen in progesterone treatment group in depression, irritablity, anxiety, mood swing, abdominal bloating, sleeplessness, felt hopeless, breast tenderness, less interest in usual activities symptoms.

Conclusion: In this study comparing progesterone therapy with placebo for PMS in women with PCOS, we found that women had much lower depression, irritability, anxiety, mood swing, abdominal bloating, sleeplessness, felt hopeless, breast tenderness, less interest in usual activities symptoms during progesterone treatment.

Keywords: Premenstrual syndrome; Polycystic ovary syndrome; Progesterone

Introduction

Premenstrual Syndrome (PMS) is defined as a group of disorders characterized by emotional and physical symptoms that occur in the lateral phase of the menstrual cycle and subside following menstruation [1]. Physical symptoms include headaches, breast tenderness, abdominal bloating, peripheral edema and general fatigue and emotional disorders include irritability, mood swings, social withdrawal, anxiety and depression [2,3]. The reported prevalence of severe PMS is variable between 3% and 24% [4,5]. Etiology of PMS remains unknown but cyclical ovarian activity and the effect of estradiol and progesterone on the neurotransmitters serotonin and Gamma-Aminobutyric Acid (GABA) appear to be key factors [6,7]. One hypothesis that the cause of PMS is the deficiency of progesterone and its derivatives [6,8,9]. Women with PMS often have an exaggerated response to hormonal changes. But there is not enough data to conclude whether or not progesterone was an effective treatment for PMS. Polycystic Ovary Syndrome (PCOS) is characterized with chronic an ovulation/oligo-ovulation. Due to this there is a distinct deficiency of progesterone and its derivatives in PCOS [10,11].

Progesterone deficiency may increase severity of PMS symptoms in PCOS but there is no study about this. And also there isn't any study that explore the prevalence of PMS in PCOS. The aim of this study was to investigate the efficacy of progesterone therapy for PMS in woman with PCOS.

Materials and Methods

This study was conducted at Izmir Ege Gynecology and Obstetrics Teaching and Research Hospital between August 2012 and April 2013. A randomized double blind controlled trial was performed on 60 women with PCOS and PMS. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is used for the diagnosis of PMS (Table 1). Diagnosis of PCOS was made by application of the Rotterdam ESHRE/ASRM criteria. According to these criteria, PCOS was diagnosed if at least 2 of the following were present: oligo/an-ovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasonography. Women who were ≥ 18 years old with PCOS and PMS and no psychiatric diagnoses in the past 2 years were included. Women with adrenal hyperplasia, hyperprolactinemia, thyroid disorder and untreated depression were excluded.

The eligible women were randomly assigned into two groups

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1- Markedly depressed mood, feelings of hopelessness or self-deprecating thoughts
2 - Marked anxiety, tension, feelings of being "keyed up" or "on edge"
3- Marked affective lability (e.g. feeling suddenly sad or tearful or increased sensitivity to rejection)
4- Persistent and marked anger or irritability or increased interpersonal conflicts
5- Decreased interest in usual activities (e.g. work. school. friends. hobbies)
6- Subjective sense of difficulty in concentrating
7- Lethargy, easy fatigability or marked lack of energy
8- Marked change in appetite, overeating or specific food cravings
9- Hypersomnia or insomnia
10- A subjective sense of being overwhelmed or out of control
11- Other physical symptoms such as breast tenderness or swelling headaches joint or muscle pain a sensation of "bloating" or weight gain

Table 1: Criteria for Premenstrual Syndrome.

using simple randomization method. In the study group (progesterone group = group A, n=30), progesterone (progestin 100 mg capsule, Kocak Farma) in a total amount of 300 mg was prescribed for a per day basis on three times a day orally, and in the control group (placebo group=group B, n=30) placebo capsules, which were completely similar to progesterone capsules were prescribed from day 15 to day 25. The severity and duration of symptoms were compared in both groups before treatment and 3 months after the beginning of treatment with Visual Analog Scala (VAS). VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks by gynecologist who gave the assessment. Participants were requested to answer questions about their recurrent experience of 16 symptoms during the premenstrual phase.

a. Research criteria for premenstrual syndrome (Table 1)

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4) (Table 1).

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation).

All participants gave written consent to participate. They were healthy, medication-free, reported regular menstrual cycles, did not use hormonal contraception, were without any current or previous history of psychiatric illnesses, had no history of gynecological pathology, were 1 year post-partum or never pregnant, and not currently breast feeding.

Data were analyzed using the Statistical Package for Social Science (SPSS, version 15.0). Kolmogorov-Smirnov test was used to test the normal distribution, Kruskal-Wallis test was used for comparisons between groups for normally distributed variables.

Results

We investigated 60 females with PMS and PCOS (mean age progesterone group/plasebo group = 26.6 ± 2.5/ 27 ± 1.8years; range = 18-35 years). Woman with PCOS are more likely than women without PCOS to be obese. The mean body mass index value was 25.1 ± 1.1/25.4 ± 1.3 kg/m². The mean age at menarche was 13.6 ± 1.3/ 12 ± 1.8 years and dysmenorrhea started at an age of 16.3 ± 1.8 (Table 2).

In terms of phenotypes of PCOS, ovulatory women with hyperandrogenism and polycyctics ovaries have a mild form of the disorder. Normal ovulation, an ovulation, oligo-ovulation can be find out in women with PCOS. Due to this every menstrual cycle has a different hormonal status that affects the psychological and somatic behaviors. Two or more premenstrual symptoms were detected in 95.5% of the participants. The most frequent symptoms are depression, anxiety, abdominal bloating, mood swings, breast tenderness (Figure 1).

Approximately 25% of the participants graded their dysmenorrheal pain as mild, 66% as severe and only 9% of the participants reported very severe menstrual pain. Patients were evaluated for 16 symptoms with VAS before and after progesterone treatment (Table 3).

Statistical significant decline was seen in progesterone treatment group in depression, irritability, anxiety, mood swing, abdominal bloating, sleeplessness, felt hopeless, breast tenderness, less interest in usual activities symptoms ($p<0,05$). Anxiety, abdominal bloating, sleeplessness and breast tenderness were much less in progesterone group than placebo group.

Conclusion

PMS creates significant impairment amongst women of working age and causes productive power loss. This makes it an important disorder to know more about it.

	Progesterone group	Placebo group	p
N	30	30	
Age (years)	26.6 ± 2.5	27 ± 1.8	>0.05
BMI (kg/m²)	25.1 ± 1.1	25.4 ± 1.3	>0.05
Cycle length (days)	38.2 ± 4.1	40 ± 4.2	>0.05
Menarche Age	13.6 ± 1.3	12 ± 1.8	>0.05
PMS Family Hisory (%)	82.5	84.5	>0.05
Kruskal-Wallis p < 0.05 statistical Significant p > 0.05 means there is no sociodemographic difference			

Table 2: Sociodemographic characteristics (mean ± SD) of both groups.

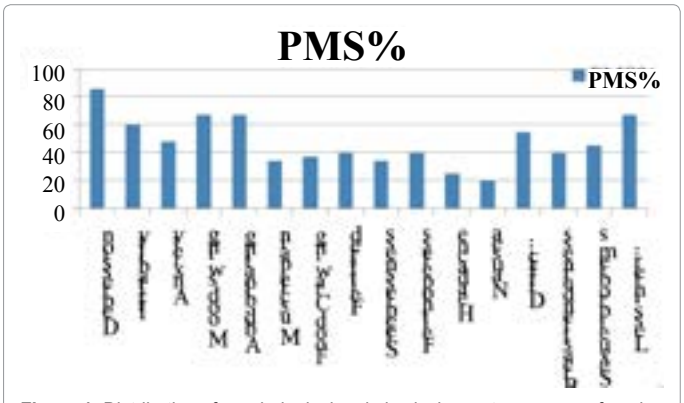

Figure 1: Distribution of psychological and physical symptoms among females with premenstrual syndrome.

	Progesterone Group(n=30)			Placebo Group (n=30)			
	VAS Before treatment	VAS After treatment	p	VAS Before treatment	VAS After treatment	p	p
Depression	4.78 ± 1.28	2.34 ± 1.23	0.001	4.56 ± 1.38	2.98 ± 1.60	0.003	0.06
Irritability	3.77 ± 0.65	1.55 ± 0.88	0.001	3.78 ± 1.34	1.21 ± 0.44	0.001	0.4
Anxiety	3.48 ± 1.68	1.33 ± 0.12	0.001	3.11 ± 1.54	2.78 ± 1.28	0.06	**0.001**
Mood swing	5.14 ± 1.08	3.23 ± 1.28	0.001	5.71 ± 1.18	2.77 ± 1.39	0.001	0.4
Abdominal bloating	6.18 ± 2.21	2.78 ± 1.18	0.001	5.63 ± 2.38	4.78 ± 2.27	0.3	**0.001**
Muscle pain	3.13 ± 1.45	3.41 ± 1.6	0.1	3.08 ± 1.21	2.78 ± 1.28	0.5	0.3
Food Craving	3.79 ± 0.78	3.22 ± 1.4	0.06	3.81 ± 1.12	2.98 ± 1.73	0.6	0.1
Felt tired	2.58 ± 1.62	2.21 ± 1.2	0.06	2.55 ± 1.54	1.78 ± 0.28	0.001	0.001
Sleeplessness	2.31 ± 1.12	1.64 ± 1.23	0.001	2.48 ± 1.31	2.18 ± 1.17	0.1	**0.001**
Felt hopeless	2.55 ± 1.48	1.18 ± 0.78	0.001	2.74 ± 1.23	1.58 ± 1.78	0.001	0.2
Headache	3.23 ± 1.77	3.38 ± 1.44	0.1	3.78 ± 1.48	3.12 ± 1.86	0.2	0.6
Nausea	3.18 ± 1.48	2.68 ± 1.79	0.07	3.88 ± 1.32	2.11 ± 1.58	0.08	0.06
Difficulty concentrating	5.71 ± 2.58	4.78 ± 1.28	0.04	5.44 ± 2.35	4.78 ± 1.24	0.04	0.06
Breast tenderness	5.78 ± 2.28	2.28 ± 1.44	0.001	5.78 ± 2.18	4.78 ± 1.58	0.07	**0.001**
Sexual problems	1.66 ± 1.08	1.38 ± 1.18	0.5	1.33 ± 0.78	1.28 ± 1.08	0.05	0.06
Less interest in usual activities	4.69 ± 2.19	3.78 ± 1.28	0.001	4.88 ± 2.22	3.28 ± 1.28	0.001	0.05

VAS: Visual Anolog Skala
Kruskal-Wallis Test $p < 0.05$ statistical significant

Table 3: Statistical evaluation of VAS scores.

It represent a wide group of physical and emotional symptoms. Typical emotional symptoms include anxiety, irritability, depression, mood swings, sleep disorders and loss of self control. Physical symptoms are prevalent and they include breast tenderness, weight gain, headaches, change in appetite, general aches and pain, and feeling bloated. The symptoms of PMS regularly occur during the luteal phase of the menstrual cycle and resolve by the end of menstruation [12,13]. The exact pathophysiology is unknown but ovarian hormones are thought to be responsible. GABA and serotonin pathways in the central nervous system have also been implicated in the etiology of PMS. Treatment strategies involve hormonal manipulation or targeting the response systems in the brain [14,15].

Polycystic ovary syndrome is one of the most common endocrine disorders in women of reproductive age and have substantial psychological, social, and economic consequences like PMS. The etiology of PMS and PCOS is largely unknown. But they both have endocrinological pathology. However this there isn't any study that investigate the correlations and treatment options of PMS in women with PCOS.

Normal ovulation, an ovulation, oligo-ovulation can be find out in women with PCOS.

Absence of PMS before puberty, in pregnancy and after the menopause supports the theory that cyclical ovarian activity is important. The exact pathophysiology of PMS is unknown but ovulation has to occur for symptoms to develop [14,15]. Because of this, subgroup of PCOS with normal menses were chosen for this study.

In this study we assessed the effectiveness of progesterone treatment for PMS in women with PCOS. Because of chronic anovulation/oligo-ovulation in PCOS there is a distinct progesterone deficiency that possibly cause PMS.

In this study comparing progesterone therapy with plasebo for PMS in women with PCOS, we found that women had much lower depression, irritability, anxiety, mood swing, abdominal bloating, sleeplessness, felt hopeless, breast tenderness, less interest in usual activities symptoms during progesterone treatment. And also in placebo group three months later, depression, irritability, mood swing, felt tired, hopeless showed significant improvement. We thought it caused by the psychological etiologic factors of the disease.

This is the first study which investigate progesterone treatment for PMS in PCOS patients. So more research is needed to clarify the efficacy of some of the treatment modalities for PMS such as progesterone and progestogens in women with PCOS.

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