ORIGINAL ARTICLE

Luteal Phase Estradiol & Progesterone Levels in Relation to Symptom Severity in Patients with Premenstrual Syndrome

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Abstract

Premenstrual syndrome is characterized by disturbing somatic and behavioural symptoms that develop after ovulation, reach a maximum during premenstrual days and disappear four days after the onset of menstruation. The aim of present study is to investigate the relationship between serum levels of estradiol and progesterone in luteal phase and PMS symptom severity in patients with PMS. We selected sixty young healthy adult females in the age group 15 and 30 and rated them for PMS symptoms. Daily blood samples were taken in follicular phase (5-8 days) and luteal phase(22-26 days). Serum estradiol and progesterone were analyzed using commercial RIA kit. Based on premenstrual hormone concentrations patients were divided into groups with high, normal and low hormonal levels. It was found that in females with a premenstrual increase in serum estradiol and decrease in serum progesterone levels , symptoms were 70 % and 70.6 % respectively, ($p<0.01$for both) which is statistically significant .

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Key Words

Progesterone, Estradiol, Premenstrual Syndrome, Luteal Phase

Introduction

Premenstrual syndrome or premenstrual dysphoric disorder (1) has emerged as an important reproductive health care issue. It is a disorder of non specific, somatic, physiological and behavioural symptoms recurring cyclically in premenstrual phase of the menstrual cycle which resolves completely by the end of menstruation (2). This syndrome appears to be caused by the response of CNS to factors produced by the corpus luteum (3,4). because PMS symptoms are not seen in patients with anovulatory cycles therefore the role of ovarian steroids, 17 -beta -estradiol (E2) and progesterone (P) is suspected. Currently the successful hormonal treatment of PMS is suppression of ovulation and removal of cyclical hormonal changes in luteal phase (5)

The ovarian steroids are known to have direct effects in the CNS (E2 on the glutamates and P metabolites on GABA receptors) as well as on protein synthesis via genomic action (6,7). In an attempt to elucidate this issue serum estradiol and progesterone levels were done in follicular and luteal phase of the menstrual cycle and it was seen that increased levels of estradiol and decreased levels of progesterone in the luteal phase resulted in more severe premenstrual symptoms (6) which has been demonstrated earlier by several groups. All cycles studied were ovulatory and the day of ovulation was determined as day after LH surge. They completed a questionnaire concerning their previous mental and physical health, education, marital status, and PMS history. Informed consent was taken from each participant.

Material & Methods

60 females of age group 15 - 30 years volunteered as subjects for thepresent study from the Gynecology OPD, B. J .Medical College and Hospital,Ahmedabad. Consent for analysis was obtained from all participants.Every morning, the females completed the symptom rating scale. In total five negative symptoms (depression, anxiety, tension, fatigue and irritability) and three somatic signs (breast tenderness, swelling and headache) were rated. For each symptom, subjects marked on a 10 cm long scale (graded 0-10), the severity of suffered symptom. 0 was taken as complete absence and 10 as maximum severity of symptoms.

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Table 1. Comparison of Symptoms in Normal, Increased and Decreased Levels of Serum Estradiol

Serum estradiol levels(luteal phase)	Symptoms present	Symptoms absent	Total
Increased	14	6	20
%	70	30	100
Normal	10	20	30
%	33.4	66.6	100.0
Decreased	4	6	10
%	40.0	60.0	100.0

Table 2 . Comparison of Symptoms in Normal, Increased and Decreased Levels of Serum Progesterone

Serum progesterone levels	Symptoms present	Symptoms absent	Total
Increased	6	5	11
%	54.5	45.5	100
Normal	14	18	32
%	43.7	56.3	100
Decreased	12	5	17
%	70.6	29.4	100

Blood samples were collected from all the females in follicular (11-15th day) and luteal phases (17 - 22nd) day of the cycles and assayed for serum estradiol and progesterone. Assay was done using commercially available RIA kit DSL 4000. The sensitivity for serum progesterone was 0.10 ng/ml. The progesterone antiserum is taken from rabbit. Cross reactivity of the antiserum with 5alpha-pregnane 3,20-dione, 20? dihydroprogesterone and corticosterone was 8, 0.35 and 0 .35 % respectively and with cortisol, pregnenolone, estradiol and testosterone was non detectable (<0.1 %).

RIA kit (DSL-4400) was used for estradiol. The sensitivity for serum estradiol was 4.7 pg/ml .The estradiol antiserum showed cross reactivity with estrone, 17-beta estradiol-3-glucuronide to the extent of 3.40 and 1.80% and cross reactivity with testosterone and diethylstilbesterol was non -detectable (<0.01 %).

Statistical Analysis

Based on premenstrual hormone concentration and using the median split method, patients were divided into groups with high, normal or low hormonal levels .Using chi-square test, 'p` value was estimated and data was analysed. A 'p' value of < 0.05 was taken as the level of significance.

Results

The symptom parameters showed decreased severity during first three days and increased severity after ovulation. The patients with luteal phase E2 concentration were compared with those of normal and low E2 levels (*table1*) more PMS symptoms were expressed in high E2 group. Mean E2 level were seen to be 508± 30 pg/ml.

It was seen that in females with a premenstrual increase in serum estradiol, symptoms were 70% compared to a premenstrual decrease in levels. (Normal levels - 10- 35.5pg/ml) Chi-square value is 6.67 and 'p' value is <0.01 which is significant. (*Table 1*)The patients with high luteal phase progesterone were compared with those who had normal or low levels in terms of symptom severity. More PMS symptoms were expressed in low P group (*table 2*). Mean P levels were seen to be 26.7±4 (normal; levels 0.20-25 ng/ml). It was found that in females with a decreased luteal phase serum progesterone levels, symptoms were 70.6 % compared to increased or normal levels. Chi- square value is 7.13 and p value is < 0.01 which is statistically significant (*table 2*).

Discussion

The present study demonstrated that there is a

remarkable increase in PMS symptoms with increase in luteal phase levels of estrogen and decrease in progesterone. The serum concentration of E2 and P showed a high degree of correlation to the occurrence of PMS symptoms (8,9,10). In general, E2 exerts excitatory action and P exerts inhibitory effects on CNS (11,12) but E2 administration in luteal phase resulted in a more severe negative mood compared to placebo according to a previous study (7). The ovarian steroids are known to have direct effects on the CNS (E2 on glutamate and P on GABA receptors) (13,14) as well as on protein synthesis via genomic action.It is also seen according to earlier studies conducted(15,16) that 5-alpha-pregnone,20 which is a progesterone metabolite with anxiolytic properties, acts as a GABA receptor agonist and might be important for the well being of the patients.

Progesterone metabolites specially allopregnanolone are neuroactive and readily cross blood brain barrier .They act by GABA system in the brain and have similar effects as benzodiazepines, barbiturates and alcohol (17). An abnormal neurotransmitter response to the multifactorial variation of steroids (18) secreted by the ovary is more likely to be etiological basis of PMS symptoms.According to some studies conducted earlier , metabolic precursor of progesterone, pregnanolone sulphate is active in CNS by interacting with GABA gated chloride channels in an antagonistic fashion (19,20). Pregnanolone sulphate diminishes chloride conductance by reducing the channel opening frequency (21,22,23).

In conclusion high levels of estradiol and low levels of progesterone in the luteal phase seems to be responsible for the severity of PMS symptoms.

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