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PLASMA ATRIAL NATRIURETIC PEPTIDE LEVELS IN NORMAL MENSTRUAL CYCLE AND PREMENSTRUAL TENSION SYNDROME.

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Abstract

Atrial natriuretic peptide (ANP) concentrations were determined in 20 women: 10 women with premenstrual tension syndrome (PMS) and 10 comparable asymptomatic women. The asymptomatic women showed significant decrease while the PMS group showed insignificant change in mean ANP concentration in the midluteal phase compared to the level in the follicular phase. The mean midluteal ANP concentration was found to be significantly higher in the PMS group ($P < 0.05$) Mean plasma aldosterone concentration was found to increase significantly in the luteal phase in both groups with lower rise in the control group. No significant difference was noted in both groups regarding serum estradiol and progesterone in both follicular and luteal phases.

Introduction

One of the suggested mechanisms of premenstrual tension syndrome (PMS) is water and sodium retention (O'Brien, 1987). It is probable that an exaggerated response to the hormonal changes of the ovarian cycle is responsible for the diverse physical and psychological symptoms in PMS, as inhibition of ovulation appears to abolish these symptoms (Muse et al., 1984).

Human atrial natriuretic peptide (ANP), has diuretic, renin, angiotensin and aldosterone antagonistic Properties. It is secreted in response to increase in intravascular volume and sodium volume loading (Atlas and Laragh, 1986). While the attention has focused recently on the role of ANP in obstetrics, little is known about its
role in gynecology and very little is known about its role in the normal menstrual cycle and PMS.

Davidson et al. (1988), reported no variation in ANP concentration during the menstrual cycle in women with PMS. In contrast to these findings, Hussain et al. (1990) found significant fall in ANP in the midluteal phase compared to the level in the follicular phase in women with PMS when compared with the asymptomatic women.

Aim of the study:
The aim of this study was to investigate the possibility that the concentration of ANP may be altered in premenstrual syndrome.

Subjects, materials and methods:

1- Subjects:
This study was carried out on twenty women recruited from the gynecological outpatient clinic of Benha University Hospital from July 1993 to June 1994. These women were divided into 2 groups, each of 10 women. The first group (study group): women suffering from premenstrual tension syndrome and the second one (control group) were asymptomatic women.

No woman in the study group suffered from cardiovascular or renal disease or had a history of psychiatric illness. None had used a medication for at least 2 months before recruitment to the study and all were on unrestricted diet.

All women with PMS were symptom free for 2 weeks after onset of menstruation. This was important to establish the diagnosis (Chuong and Kinch, 1990) and to distinguish the condition from mere exacerbation of some chronic conditions such as idiopathic edema, fibrocystic breast disease, endogenous depression or anxiety neurosis (Reid and Yen, 1983).

In the midfollicular and midluteal phases, body weight was recorded and blood pressure was measured. In addition, prospective symptom assessment was made for depression, irritability, headache, breast pain and bloatedness.
2- **Materials**:  
Blood samples were taken in the follicular phase (day 6-9) and midluteal phase (day 20-23) of the menstrual cycle from each woman. Fasting blood sample was collected into a chilled syringe and divided into two samples:

a- **Plasma Sample**:  
About 4 ml blood was transferred into a polypropylene tube containing EDTA (1 mg/ml of blood) and Aprotinine (500 KIU/ml of blood) at 0°C. Blood was centrifuged at 3000 Xg for 15 minutes at 0°C. Clear unhaemolysed plasma was separated and stored at -20°C until estimation of the plasma atrial natriuretic peptide level.

**Serum sample**:  
About 4 ml blood was transferred into a centrifuge tube and incubated at 37°C for clotting to occur. Clear unhaemolysed serum was separated by centrifugation and stored at -20°C until estimation of:

- Serum estradiol (E$_2$).
- Serum progesterone.
- Serum aldosterone.

**Laboratory material**:  
Gamma scintillation counter, Vortex mixture, water bath, automatic pipettes, Kit materials and reagents for estimation of plasma atrial natriuretic peptide and serum estradiol, progesterone and aldosterone by radioimmunoassay (RIA).

3- **Methods**:  
Plasma ANP was determined by the methods of Sagnella and Macgregor (1984). Serum estradiol and progesterone were determined by the method of Abraham (1976) and Abraham et al. (1971). Serum aldosterone was determined by the method of Abraham et al. (1977).

Statistical comparison of the data of both groups were done using the unpaired student test. For comparison within groups, paired t test was applied.

**Results**  
Comparison of the clinical characteristics of PMS and control groups is shown in table (1). No significant difference was found. This means that both groups were comparable.
The mean serum aldosterone concentration in the luteal phase was significantly higher than that in the follicular phase in both groups (P < 0.05). No significant difference was noted on comparing the mean levels of both groups.

The differences in serum oestradiol and progesterone mean values between both groups were found to be non significant in follicular and luteal phases. However, the differences between follicular and luteal phases serum progesterone were found to be highly significant in each group (P < 0.001).

Table 1: Clinical characteristics of the PMS group and asymptomatic (Control) group:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group</th>
<th>PMS group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.1 ± 5.4</td>
<td>24.3 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>28.1 ± 0.9</td>
<td>27.3 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of menses (days)</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kgm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>62.5 ± 5.7</td>
<td>64.6 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Luteal</td>
<td>62.6 ± 5.1</td>
<td>64.8 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>85.3 ± 6.5</td>
<td>90.3 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Luteal</td>
<td>87.3 ± 5.5</td>
<td>91.2 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS = non significant.
Table 2: Comparison between plasma ANP and serum aldosterone, estradiol and progesterone values in the follicular and luteal phases of the PMS and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>PMS group</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma ANP (pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>30.3 ± 8.5</td>
<td>27.7 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Luteal</td>
<td>20.1 ± 7.4</td>
<td>32.1 ± 6.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Serum aldosterone (Pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>159.6 ± 63.2</td>
<td>155.5 ± 62.5</td>
<td>NS</td>
</tr>
<tr>
<td>Luteal</td>
<td>223.2 ± 71.2</td>
<td>240.9 ± 90.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Serum estradiol (Pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>166 ± 67.7</td>
<td>155.8 ± 53.5</td>
<td>NS</td>
</tr>
<tr>
<td>Luteal</td>
<td>154 ± 57.5</td>
<td>148.5 ± 50.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Serum progesterone (ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>1.94 ± 0.5</td>
<td>2.0 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Luteal</td>
<td>12.4 ± 7.2</td>
<td>9.9 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

NS = non significant.

**Discussion**

This study compares ANP concentration in women with well defined PMS and asymptomatic women. The mean plasma ANP concentration decreased significantly in the luteal phase compared to the mean concentration in the follicular phase in the asymptomatic group. The reduced level of plasma ANP could be a compensatory response to the natriuretic effect of the increased plasma Progesterone in the luteal phase and this agrees with the results of Jensen et al. (1989). While both Clark et al. (1990) and Hussain et al. (1990) found no significant change.
Insignificant increase in the mean plasma ANP Level in the luteal phase was found in the PMS group. It was found to be significantly higher than the luteal level in the asymptomatic group. Davidson et al. (1988) showed no variation in ANP during the cycle. It was not controlled study comparing PMS women with asymptomatic women while Hussain et al. (1990) found significant decrease in the midluteal phase compared to the level in the follicular phase which was contrary to what they had expected and they suggested that this might indicate either lower plasma volume or decrease in the total body sodium content or both.

Aldosterone levels were found to be higher in the luteal phase of the menstrual cycle in both PMS and control groups and a lower rise was found in the asymptomatic group. O'Brien et al. (1979) and Munday et al., (1981), reported increased aldosterone concentrations in both asymptomatic and PMS groups in the luteal phase. On the other hand, Davidson et al., (1988) found no significant change in aldosterone concentration in the luteal phase in PMS group.

The sodium retaining effect of aldosterone is opposed by ANP and the higher aldosterone levels in the luteal phase may be secondary to the natriuretic effect of progesterone. Thus the rise in ANP in the midluteal phase in PMS group may be explained by the slight increase in aldosterone secretion (Janowsky et al., 1973).

The results of serum oestradiol and progesterone indicate that they have no definite value in the pathogenesis of PMS.

The inconsistent findings of the relatively few studies that dealt with the ANP concentration in PMS indicates the need for further well controlled larger studies, using multiple samples that cover the various stages of the menstrual cycle.

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