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Plasma Calcium Ions and Some Cardiovascular Changes During Phases of Menstrual Cycle in Young Premenopausal Nigerian Women

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Abstract: Women during menstrual cycle have demonstrated variability in cardiovascular responses, including flow mediated dilatation and calcium levels in cervical secretions. The experiment was designed to study the relationship between plasma calcium ions and some cardiovascular changes during the phases of menstrual cycle. Twenty young women aged 19-24 years with menstrual cycles that were regular and 27-30 days in length participated in the study. Venous blood sample was collected for plasma Ca^{2+} estimate using colometric method and callidy blue reagent and glycoetherdiamine as diluting agent. Systolic Blood Pressure (SBP) increased from 113.40±4.73 mmHg to 118.53±3.42 during the early follicular to the periovulatory phase. The difference is statistically significant ($p<0.05$). There was no statistical difference in the level of Diastolic Blood Pressure (DBP) measured across the menstrual cycle. The Heart Rate (HR) increased from 74.40±5.03mmHg during the early follicular phase to 86.73±8.24 mmHg during the periovulatory phase and then reduced to 90.73±8.96 mmHg during the mid-luteal phase. Both the increase and subsequent decrease were statistically significant ($p<0.05$). Plasma Ca^{2+} concentration peaked at periovulatory phase i.e. concentration of 9.85±0.41 mg dL^{-1} compare to 8.65±0.61 mg dL^{-1} during the early follicular phase ($p<0.005$). and then fell to 9.25±0.75 mg dL^{-1} during the mid-luteal phase ($p<0.05$). The result shows a positive relationship between systolic blood pressure and plasma Ca^{2+} in pre-menopausal women across the menstrual cycle with both of them peaking at periovulatory phase..

Key words: Plasma calcium ions, menstrual cycle, blood pressure, Nigerian women

INTRODUCTION

Women during the menstrual cycle have demonstrated variability in cardiovascular responses, including flow-mediated dilatation (Hashimoto *et al*., 1995; English *et al*., 1998; Karrano *et al*., 1996), arterial distensibility (Giannattasio *et al*., 1999), sympathetic outflow (Minson *et al*., 2000), α_2-adrenergic responses to agonists (Freedman and Girgis, 2000), antioxidant enzymes activities (Ha and Smith, 2003), immune activities (Shakhar *et al*., 2000) and calcium levels in cervical secretions (Gorodeski,1996). A positive correlation between the total concentration of calcium in plasma and blood pressure has been reported (Bulpitt *et al*., 1976; Kesteloot and Geboers, 1982; Robinson *et al*., 1982), though a higher intake of calcium is known to decrease blood pressure (Kesteloot and Joossens, 1988).

Oestrogen therapy in postmenopausal women decreases the risk of coronary atherosclerosis and coronary artery diseases (Bush *et al*., 1987; Guetta and Cannon, 1996). Many of the beneficial effects of exogenous oestrogen administration may be related to an increase in serum level of High Density Lipoprotein Cholesterol (HDLP) and a reduction in serum level of Low Density Lipoprotein Cholesterol (LDLP) (Bush *et al*., 1987; Guetta and Cannon, 1996), since estrogen may also have direct action on the peripheral vasculature and myocardium of the heart. 17β-esrtadiol increases nitric oxide release from coronary and aortic vascular endothelium of rabbits and directly relaxes coronary and aortic vascular smooth muscles (Ma *et al*., 1997a), facilitating both histamine- and serotonin-stimulated nitric oxide release (Ma *et al*., 1997b) and increases endothelial nitric oxide synthase (Weiner *et al*., 1994). Exposures to 17β-esrtadiol inhibit calcium ion entry into both rabbit coronary vascular smooth muscle and ventricular myocytes in the male guinea pigs. Oestrogen reduces plasma calcium and the difference in concentration of serum ionized calcium between young men and women have been observed (Roberts, 1981).

Differences in the pattern of cyclical changes in calcium and vitamin D metabolism across the menstrual

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cycles have been demonstrated in women with Premenstrual Dysphoric Disorders (PPMD) as compared to asymptomatic controls (Thys-Jacobs *et al.*, 2007). This experiment was designed to study the relationship between plasma calcium ions and some cardiovascular changes during the phases of menstrual cycle in young Nigerian pre-menopausal women.

MATERIALS AND METHODS

All the procedure was carried out according to the University of Ilorin guidelines of the Medical Ethics Committee for the use of humans in experiment. Subjects' informed consent was obtained. Twenty young women, who were students of University of Ilorin, participated in the study. They were aged between 19-24 years with menstrual cycles that were regular and 27-30 days in length. Inclusion criteria for the study were the following:

- Maintaining regular menstrual cycles of 27-30 days, with the cycle length not changing by more than two days for the three prior months.
- Not taking any type of prescribed medication including oral contraceptives for at least one year prior to study.
- Maintaining a stable body weight with a desirable body mass index (18-25 kg m^{-2}).
- Not taking alcohol.
- Non-smoking and non-dieting.
- No past or ongoing chronic illness.
- Not pregnant or lactating for one year prior to the study.
- Not exercising for more than 60 min a day or 7 h a week.

All the subjects were also certified medically fit by the university clinic physician. They had no breakfast and abstained from strenuous exercise before the study.

Height and weight were recorded and Body Mass Index (BMI, kg m^{-2}) was calculated. Height was measured without shoes using a standiometer that is a non-stretchable tape attached to a vertical flat surface (wall), with a right-angle headboard. A beam scale with non-detachable weight was used to measure weight with clothes but no shoes. Blood pressure and the heart rate were measured using the electronic digital blood pressure metre (UA-751).

Blood collection: A total of 5 m of venous blood was obtained from each subject via venepuncture using lithium heparinised tubes. Blood collections for each subject were performed at approximately the same time of the day throughout the study period to reduce variability within each individual. Immediately after the collection, plasma and erythrocytes were separated by centrifugation. Centrifuged samples were stored at-4°C, until analysis was done. Plasma Ca^{2+} was determined by colometric method using callidyl blue reagent and Glycohetherdiamine Tetraacetic Acid (GEDTA) as diluting agent.

Data analysis: For statistical data comparisons, data were evaluated by one-way ANOVA, followed by least significant differences tests. All values are given as mean ±S.E.M with n values indicating the number of subjects analyzed. p values <0.05 are considered significant.

RESULTS

The average age of the subjects was 21.6±0.02 years, weight was 53.7±2.3 Kg, the height was 1.64±0.12m, while Body Mass Index (BMI) was found to be 19.97±1.6 Kg m^{-2}. The average menstrual cycle length for the subjects was 28.4±0.3 days (Table 1).

Systolic Blood Pressure (SBP) increased from 113.40±4.73 mmHg to 118.53±3.42 during the early follicular to the periovulatory phase. The difference was statistically significant ($p<0.05$) and then fell to 114.67±4.56 mmHg. The reduction was not statistically significant ($p = 0.12$). There was no statistical difference in the level of Diastolic Blood Pressure (DBP) measured across the menstrual cycle. The Heart Rate (HR) increased from 74.40±5.03mmHg during the early follicular phase to 86.73±8.24 mmHg during the periovulatory phase. The

Table 1: Age, anthropometric data and estimated menstrual cycle length for subjects at enrollment to the study

Characteristics	Mean±S.E.M
Age (years)	21.6±0.2
Weight (kg)	53.7±2.3
Height (m)	1.64±0.12
BMI (kg m^{-2})	19.97±1.6
Cycle length (d)	28.4±0.3

Table 2: Change in estimates of systolic and diastolic blood pressures (SBP and DBP), Heart Rate and Plasma Calcium concentration (Ca^{2+}) during the early Follicular (EF), Periovulatory (PO) and Mid-Luteal (ML) phases of menstrual cycle

	Phases of menstrual cycle		
	Early Follicular	Periovulatory	Mid-Luteal
Systolic blood pressure (mmHg)	113.40±4.73^{a}	118.53±3.42^{b}	114.67±4.56^{ab}
Diastolic blood pressure (mmHg)	71.67±4.30	72.67±5.52	71.20±4.74
Heart rate (beats min^{-1})	74.40±5.03^{a}	86.73±8.24	90.73±8.96
Plasma Ca^{2+}(mg dL^{-1})	8.65±0.61^{a}	9.85±0.41^{b}	9.25±0.75^{c}

Values are mean±S.E.M, n=20, different superscripts horizontally indicates $p<0.05$

increase was statistically significant ($p<0.05$). The HR then reduced to 90.73±8.96 mmHg during the mid-luteal phase. The reduction was significant ($p<0.05$). Plasma Ca^{2+} concentration peaked at periovulatory phase i.e. concentration of 9.85±0.41 mg dL^{-1} compare to 8.65±0.61 mg dL^{-1} during the early follicular phase. The increment was statistically significant ($p<0.005$). The concentration of plasma Ca^{2+} then fell to 9.25±0.75 mg dL^{-1} during the mid-luteal phase. The reduction was statistically significant ($p<0.05$) (Table 2).

DISCUSSION

The results of this study demonstrate that the measured cardiovascular parameters and plasma Ca^{2+} showed distinct variations during the menstrual cycle in healthy young premenopausal women. There is a positive relationship between plasma Ca^{2+} and SBP. Plasma Ca^{2+} and SBP increased significantly from lowest level during the early follicular phase to a maximum level during the periovulatory phase, which is the period of maximum oestrogen secretion during the menstrual cycle. Thereafter, the plasma Ca^{2+} decreased to an intermediate level during the Mid-Luteal (ML) phase during which oestrogen secretion is usually reached a midpoint of concentration for the cycle. The time of greatest change for each parameter was between Early Follicular (EF) and the Periovulatory (PO) phases. Earlier study by Soladoye (1998) had demonstrated that SBP is highest during the PO phase of menstrual cycle.

The relationship between the total concentration of calcium in serum and blood pressure has been reported to have positive correlation between serum calcium and systolic blood pressure (Bulpitt *et al*., 1976; Fogh-Andersen *et al*., 1984). In our present study, we observed positive correlation between plasma calcium ions and SBP but not DBP. Green and Jucha (1987) also found positive correlation between serum Ca^{2+} and SBP and not DBP. Apart from plasma calcium, other factors that might be responsible for the observed increase in SBP at the period of peak oestrogen secretion could be haemodilution as a result of water retention caused by oestrogen.

Cardiovascular effects of oestrogen have been contradictory. While Schaible *et al*. (1984) observed a positive inotropic effect, Raddino *et al*. (1986, 1989) reported a negative inotropic action on acute exposure of isolated rabbit heart to oestrogen and vascular smooth muscle.

There was no significant relationship between plasma calcium and DBP across the menstrual cycle. This is similar to the result obtained by Bulpitt *et al*. (1976) which showed no positive relationship between serum calcium and DBP. There was a positive correlation between the HR and plasma calcium. The increased HR with increased plasma Ca^{2+} could be due to increased activity of L-type Ca^{2+} channels in the heart muscle and increased nor adrenaline secretion during midcycle (Chan *et al*., 2001). In the mid-luteal phase, there is further increase in heart rate even though Ca^{2+} level has fallen. The increase is not statistically significant. The reason for this might be due to the presence of progesterone which is known to increase body temperature and metabolic process. Heart rate is increased by about 18 beats per 1°C increase in body temperature. The effect of progesterone on heart rate might override that of Ca^{2+} and oestrogen.

The observed variation in Ca^{2+} is consistent with that of Thys-Jacobs and Alvir (1985) and Thys-Jacob *et al*. (2007) who observed highest concentration of plasma Ca^{2+} during the periovulatory period of menstrual cycle and significant variations across the menstrual cycle between asymptomatic and women with PPMD. They also observed increased midcycle concentration of parathyroid hormone and 1, 25, dihydroxycholecalciferol, which are hormones that increased plasma Ca^{2+}. Pitkin *et al*. (1978) also observed positive correlation between plasma Ca^{2+} and parathyroid hormone through menstrual cycle. That plasma Ca^{2+} and Parathyroid Hormone (PTH) rose through the follicular phase of menstrual cycle to peak at periovulatory phase.

Our study suggests that phase of menstrual cycle should be considered when assessing plasma Ca^{2+} in premenopausal women because the fluctuations is significant even though it is within the normal range. Likewise, the phase of menstrual cycle should also be considered when determining the Systolic Blood Pressure (SBP) and Heart Rate (HR) in premenopausal women because of the significant change in their levels.

CONCLUSION

Our study shows that there is a positive relationship between SBP and plasma Ca^{2+} in pre-menopausal women across the menstrual cycle with both of them peaking at periovulatory phase. Heart rate also increased through the follicular phase, but further increased during the luteal phase, which may be due to the fact that other factors such as progesterone and body temperature may affect the heart rate positively.

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