PHASIC VARIATION OF SERUM CALCIUM AND MAGNESIUM IN MENSTRUAL CYCLE

Vani Lanke*, Santhi Vadugu
*Assistant Professor, Department of Physiology, Guntur Medical College, Guntur - Pin-522004, A.P., India.

AIM: Estimation of serum calcium and magnesium serially during menstrual, proliferative and secretory phases of menstrual cycle.

METHOD: Serum calcium and magnesium were estimated in 30 healthy student volunteers with regular menstrual cycles by Sysmex chemical analyzer.

RESULT: The results were analysed by student t-test with the help of Graphpad software Quickcalc t-test calculator which showed significant cyclic variation but within physiological limits. From menstrual phase to proliferative phase, serum calcium levels increased (P-value 0.051) which is statistically significant. But from proliferative phase to secretory phase, calcium levels decreased (P-value 0.052). Whereas results for serum magnesium obtained were exactly opposite to that for serum calcium levels. Serum magnesium levels decreased from menstrual phase to proliferative phase (P-value 0.055) which is statistically significant and from proliferative phase to secretory phase serum magnesium levels increased (P-value 0.057). These changes in serum electrolytes may be attributed to the cyclic variations of ovarian hormones - estrogen and progesterone. Serum Ca2+/Mg2+ ratio increased from menstrual to proliferative phase and then decreased from proliferative to secretory phase.

CONCLUSION: The cyclical changes in serum calcium and magnesium may produce changes in fluid and electrolyte balance responsible for premenstrual syndrome. This variation though is within physiological limits, gives indication for correction of necessary electrolytes for relief of pre-menstrual distress experienced by some women.

Introduction

Menstrual cycle comprising of proliferation, secretion and denudation is well in comparison with the forces of creation, preservation and destruction. Menstrual cycle is important in that it is necessary for creating and perpetuating humankind.

The word menstruation is derived from Latin word menses meaning month, which relates to Greek word mene (moon) and English words month and moon. Human menstrual cycle is a cyclical phenomenon which is inevitable in almost every woman's life. The start of this cycle marks the onset of active reproductive life. It is accompanied by various structural and hormonal changes which occurs in a sequential pattern.

The only visible external sign is periodic vaginal discharge of blood along with shed off degenerated uterine mucosa and endometrium. [1] This vaginal bleeding occurs every month for about 3-5 days and hence is aptly called periods or menstruation. [1,2,3,4]

This phenomenon is controlled by cyclical fluctuations of certain hormones like FSH and LH of pituitary gland and also of sex hormones-oestrogen and progesterone. This cyclical process is controlled by HPO-axis and pulsatile GnRH release. The pulsatile GnRH release is necessary for normal secretion of gonadotropins and is modified by gonadal steroid hormones.

In the initial half of the ovarian cycle, there is more of oestrogen which is responsible for re-epithelialisation of desquamated endometrium and subsequent proliferation and growth of various cells, glands and blood vessels accounting for increased thickness of endometrium. This phase is called proliferative phase.

Ovulation is followed by secretory phase, which is characterized by increased levels of estrogen and progesterone, but predominantly progesterone. Oestrogen causes proliferation of endometrium while progesterone causes secretory development. The glands become more tortuous, secretory substances accumulate in the theca and granulosa cells and there is increased blood supply. [5]

So the endometrium becomes secretory, containing stored nutrients to provide favourable conditions for implantation of fertilized ovum. Corpus luteum progresses through stages of proliferation, enlargement, secretion and degeneration in a sequence.

* Corresponding Author: Dr. Vani Lanke,
Assistant Professor of Physiology,
Guntur Medical College,
Guntur, A.P.
PIN 522004.
E mail address: lankevan16@gmail.com

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During menstruation which is brought about by reduced progesterone and also by estrogen, there occurs initially vasospasm of tortuous endometrial blood vessels [6]. This along with loss of hormonal stimulation causes necrosis in endometrium with seeping of blood into endometrial layers and ultimately necrotic endometrium is sloughed off in layers along with blood which are expelled out of the uterus.

Establishment of the normal menstrual cycle is the ultimate goal of development of the HPO circuit. For this purpose, two simple aspects involved are the development of a mature negative feedback system and a positive feedback mechanism which is the final event of pubertal maturation allows regular LH surges and ovulation. [7] The only one requisite for an operational positive feedback is the presence of an adult pulsatile secretion of GnRH with one pulse of 90-120 minutes.

Now it is recognized that menstrual cycle brings about changes in various systems. Changes in hematological parameters and blood cell population do occur during different phases of menstrual cycle.

Naturally occurring fluctuations in sex steroid hormone levels during menstrual cycle provides a basis for analyzing interactions between steroid hormones and hematological parameters.

In premenstrual days, women do suffer changes in fluid and electrolyte balance. Sex steroids are known to have effects on water and electrolyte balance. So efforts are made to note the changes in serum calcium and magnesium during various phases of menstrual cycle.

The majority of calcium in the body is stored in the bones but it is the free, ionized calcium in the cells and extracellular fluids that fulfills physiological roles in cell-signaling, nerve function, excitation-contraction coupling causing muscle contraction and blood coagulation.

The calcium levels in blood are influenced by parathyroid hormone and Vitamin D. Parathormone elevates calcium levels in blood. For normal parathyroid secretory responses magnesium is required. Magnesium is necessary for carbohydrate metabolism.

Variations in serum calcium and magnesium accounts for the alterations in hemostatic responses, coagulation and electrolyte balance. The present study was conducted to know the phasic variations of these serum electrolytes during menstrual cycle.

MATERIALS AND METHODS

Thirty young, healthy, subjects of reproductive age group (17-22 years) and with regular menstrual cycles [1,2,3,4] were included in the study after excluding pregnancy, anemia, endocrine, gynaecological and hemostatic disorders and also infection.

Prior to the study, each subject was informed the aims and objectives of the research method and also the experimental methods to be employed. Their consent was obtained. For the best co-operation, all the subjects were well motivated. The subjects were followed during a single menstrual cycle.

Collection of Blood Sample:

The procedure was explained to the subject and blood sample was collected from antecubital vein under strict aseptic conditions using sterile needle. The collected blood was expelled gently into the sterile bottle with anticoagulant.

Three blood samples were taken during
(i) menses (within 48 hours)
(ii) proliferative phase (6-9 days)
(iii) secretory phase (22-24 days).

With each sample serum calcium and magnesium were estimated. In the present study Ca and Mg levels were analysed by Sysmex chemical analyzer (Indian made).

ANALYSIS OF RESULTS

Data was interpreted as mean and standard deviation (±S.D.). Means were compared between two groups by student’s unpaired t-test using PSPP software (Graphpad software Quickcalcs t-test calculator).

SERUM CALCULUM:

The mean serum calcium levels in menstrual phase, proliferative phase and secretory phase as shown in table-1 are (9.799 ± 0.177), (9.922±0.287) and (9.706± 0.522) respectively.

So, serum calcium levels are elevated in proliferative phase when compared to menstrual phase with a p value 0.051 which is statistically significant. Serum calcium levels are decreased in secretory phase when compared to proliferative phase with a p value 0.052 which is just statistically significant.

Ca²⁺/Mg²⁺ ratio:

The means of Ca²⁺/Mg²⁺ ratio menstrual phase, proliferative phase and secretory phase as depicted in table-3 are (4.808 ± 0.222), (5.06 ± 1.15) and (4.901± 1.401) respectively.

So the Ca²⁺/Mg²⁺ ratio is increased during proliferative phase when compared to menstrual phase with a p value 0.005 which is not so statistically significant.

The ratio is decreased in secretory phase when compared to proliferative phase with a p value 0.03 which is just statistically significant.

Table-1. COMPARISON OF SERUM CALCIUM IN DIFFERENT PHASES OF MENSTRUAL CYCLE IN HEALTHY WOMEN.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MENSTRUAL PHASE</th>
<th>PROLIFERATIVE PHASE</th>
<th>SECRETORY PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERUM CALCIUM (Mean±S.D)</td>
<td>9.799±0.177</td>
<td>9.922±0.287*</td>
<td>9.706±0.5226</td>
</tr>
</tbody>
</table>

*a) Significantly higher as compared to the other two (P < 0.05)

COMPARISON OF SERUM MAGNESIUM IN DIFFERENT PHASES OF MENSTRUAL CYCLE IN HEALTHY WOMEN.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MENSTRUAL PHASE</th>
<th>PROLIFERATIVE PHASE</th>
<th>SECRETORY PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERUM CALCIUM (Mean±S.D)</td>
<td>2.041±0.0814</td>
<td>1.8650±0.4866</td>
<td>2.0937±0.4242*</td>
</tr>
</tbody>
</table>

*a) Significantly higher as compared to the other two (P < 0.057)
Table 3. COMPARISON OF SERUM Ca^{2+}/Mg^{2+} RATIO IN DIFFERENT PHASES OF MENSTRUAL CYCLE IN HEALTHY WOMEN.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MENSTRUAL PHASE</th>
<th>PROLIFERATIVE PHASE</th>
<th>SECRETORY PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERUM Ca^{2+}/Mg^{2+} ratio Mean±S.D)</td>
<td>4.8085±0.2224</td>
<td>5.6065±1.1553</td>
<td>4.9016±1.4011*</td>
</tr>
</tbody>
</table>

*a) Just significantly decreased (P < 0.03)

II. SERUM MAGNESIUM(mg/dl) LEVEL DURING DIFFERENT PHASES OF MENSTRUAL CYCLE

III. SERUM Ca^{2+} / SERUM Mg^{2+} RATIO DURING DIFFERENT PHASES OF MENSTRUAL CYCLE

**DISCUSSION**

The most extensively studied rhythm in women is menstrual cycle which is associated with fluctuations in various parameters corresponding to the changes in hormonal levels. There are various studies done which are correlating with and also those which differ from the present study.

When it was probed to find reasons for the differing results, it was found that the difference in blood sampling methods, the timing of sampling, the statistical methods used for analysis could have been the probable causes. The geographical, genetic, racial factors should also be kept in mind. However the wide variation in the results specify that more extensive research is to be done to substantiate the findings.

Serum calcium levels were elevated significantly during proliferative phase and decreased during secretory phase which is consistent with our study. These results were consistent with various other researches done earlier.[8,9,10,11,12,13,14,15,16] During proliferative phase, elevated levels of estrogen cause increased activity of parathyroid glands leading to accelerated calcium re-uptake and hence increased serum calcium levels.[10] Also estrogen was found to accelerate calcium uptake simultaneously decreasing its elimination.[17] It was revealed that estrogen which is the predominant hormone in proliferative phase induced hypercalcemia.[18] During secretory phase, higher levels of progesterone and comparatively lower levels of estrogen were the probable cause of low calcium levels during that phase.[8,19,20]

It was observed that there was increase in systolic B.P. and heart rate from menstrual phase to proliferative phase and subsequent decrease in secretory phase with corresponding variation in serum calcium levels.[21]

Significant association was found between lowered serum calcium and serum magnesium levels in the premenstrual phase and PMS.[22] Withdrawal of estrogen lead to a significant loss of bone calcium.[23]

In the present study, the serum magnesium levels were elevated during menses and decreased during proliferative phase with subsequent decrease in secretory phase, which is consistent with various other studies.[8,16,24] The elevated estrogen levels during proliferative phase, by its action on PTH decreases re-absorption of magnesium by the renal tubules due to which serum magnesium levels dropped.[10,25]
Increased serum calcium levels during the proliferative phase contribute to the decreased magnesium levels [26] by exerting an effect on the cell permeability.

During secretory phase there was increased basal metabolic rate (BMR) [27] and carbohydrate utilization which requires magnesiurn and oxidative enzymes.[11]

It was found that low magnesium levels result in the constriction of cerebral and abdominal blood vessels leading to flare up of symptoms during the luteal phase of menstrual cycle.[28]

Elevated serum calcium levels contribute to the decreased magnesium levels[12] by exerting an effect on the cell permeability.

The Ca\(^{2+}\)/Mg\(^{2+}\) ratio increased from menstrual to proliferative phase [29] and decreased in secretory phase. Lower Ca\(^{2+}\)/Mg\(^{2+}\) ratio during luteal phase [13] may be related to the premenstrual syndrome complaints that some women have during this period.

The increase in Ca\(^{2+}\)/Mg\(^{2+}\) ratio coincides with peak of oestrogen and with increase in progesterone[30] which confirms that the effects of blood vessels spasm is present during menstrual period. It is also suggested that this ratio may be related to PMS complaints and with onset of migraine and tension headaches[31].

Premenstrual syndrome symptoms were relieved by vitamin D supplementation apart from magnesium infusion during second week of luteal phase,[22] probably by effective calcium levels.

Seelig MS studied on the role of magnesium and estrogen [33] in cardiovascular and bone disorders, eclampsia, migraine and premenstrual syndrome so that the disorders can be prevented by correcting the electrolyte imbalance.

PMs symptoms like fluid retention and bloating [34] were relieved by both calcium and magnesium. But magnesium had no effect on mood swings and depression. [35,36] Calcium was found to be effective in relieving neurological symptoms as well. [37,38] It was proved that calcium was effective especially during secretory and menstrual phases.[39]

Women with PMS had reduced bone mass [40] and significantly greater risk of vertebral osteoporosis [41].

It was proposed that disturbances in cellular calcium was associated with affective mood disorders[42]. Changes in extracellular concentration of calcium affects the excitability of neuromuscular tissues involved in emotional regulation [43]. Hypocalcemia is associated with irritability, anxiety and mania whereas hypercalcemia with depression[44].

The study on serum electrolytes revealed just statistically significant results necessitating further insight.

SUMMARY

Summing up the events during proliferative phase of menstrual cycle, oestrogen is the predominant hormone. Prior to ovulation, both FSH and LH rise but LH surge is more prominent and is pre-requisite for ovulation to occur.

During secretory phase, progesterone is the dominant hormone, though oestrogen is also held responsible for certain changes.

Variation in serum electrolytes during different phases of menstrual cycle which was attributable to cyclic variation of female sex hormones. Keeping in mind, the variation of serum calcium and magnesium, drugs are to be administered appropriately to yield favourable host response.

Cyclical changes in the fluid and electrolyte balance is the main cause of suffering of many women in premenstrual days, though the change is within physiological limits. By making necessary changes like calcium supplementation, magnesium infusion along with vitamin-D, the premenstrual symptoms can be relieved. The changes may necessitate small but significant alterations to the normal reference interval for the electrolytes. It indicates the necessity for correcting electrolyte imbalance and at the same time acts as an alarming signal for women with PMS who are more prone for reduced bone mass and osteoporosis later in their lives.

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