Serum calcium levels, serum magnesium levels and calcium magnesium ratios in different phases of menstrual cycle

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Abstract

Female reproductive hormone changes in the menstrual cycle affect the mineral metabolisms which in turn cause disorders in the body.

This study was aimed at evaluating serum calcium, magnesium, and Ca:Mg ratio during the follicular, ovulatory and luteal phase in 80 women (15 - 45 years).

The detailed menstrual history including basal body temperature for two consecutive cycles were recorded. The ovulation day was estimated individually from the change in basal body temperature and the phases were estimated from the individual cycle length and estimated ovulation day. The follicular, ovulatory and luteal phase blood samples were taken during Day 8 - 10, Day 14 - 16 and Day 22 - 26 respectively. The concentrations of calcium and magnesium were estimated by colorimetric method.

Serum magnesium progressively and significantly ($P < 0.01$) declined from follicular to ovulatory and then from ovulatory to luteal phase ($P < 0.05$). Serum calcium progressively and significantly ($P < 0.01$) declined from follicular to luteal phase. The Ca: Mg ratio progressively and significantly ($P < 0.01$) rose from follicular to luteal phase.

During the luteal phase, there was less decrease in calcium with relatively more decrease in magnesium, and increased Ca:Mg ratio. Therefore, menstruation related symptoms in the luteal phase can be reduced with the use of calcium supplementation containing relatively more magnesium.

Introduction

Female reproductive physiology is more complex than male reproductive physiology. Unlike essentially constant testosterone secretion and the continuous sperm production characteristic of the male, release of ova is intermittent, and secretion of female sex hormones displays wide cyclic swings. During each cycle, the tissues influenced by these sex hormones also undergo cyclic changes, the most obvious of which is the monthly menstrual cycle.

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Moreover, there are many less obvious changes taking place throughout the cycle. Almost all women have one or more of the wide range of physical, psychological or behavioral symptoms during the days prior to menstruation, and these symptoms disappear after menstruation. Therefore, these menstruation-related symptoms are usually considered as physiological changes of the ovulatory menstrual cycle.

There are growing bodies of evidence indicating that plasma calcium level was significantly lower in patients with affective symptoms than in control[1,2,3,4]. In addition, the previous studies suggest that physical symptoms are also induced by disturbances in calcium and magnesium metabolisms[5,6,7]. Calcium:magnesium ratio is important for blood vessel tone, excitation contraction coupling and synaptic transmission[8,9]. Thus, it leads to the consideration that calcium:magnesium ratio might also be implicated in symptoms during menstrual cycle.

Accordingly, it can be hypothesized that serum calcium and magnesium levels and calcium:magnesium ratio would fluctuate during different phases of the menstrual cycle. An extensive literature search has revealed very scanty data for their changes during the menstrual cycle. Our aim was to assess the changes in serum calcium and magnesium levels in reproductive aged women. We also sought to assess the calcium and magnesium ratio for supplementation purpose, to alleviate menstruation related symptoms during menstrual cycle.

Materials and Methods

The study was conducted on 80 healthy females in the age group of 15 - 45 years. The full clinical history of the subjects was noted and thorough physical examination was done. The different phases of the menstrual cycle (follicular, ovulatory and luteal phases) were determined by a detailed menstrual history including basal body temperature for two consecutive menstrual cycles.

Each subject was explained the aim and the method of the study. The written informed consent was obtained from all volunteered subjects individually. The subjects were instructed to take oral temperature measurement immediately after waking up, before taking any hot/cold drink in the morning. The day of ovulation was estimated individually from the change in basal body temperature recorded for previous two consecutive menstrual cycles. The phases of the menstrual cycle were estimated individually from the cycle length and the estimated day of ovulation.

As the follicular phase sample, blood was collected at 4 to 6 days - depending on the individual cycle length - before the estimated day of ovulation. The ovulatory phase sample was taken at the estimated day of ovulation and the following two days. The luteal phase sample was taken at 8 to 12 days after the estimated day of ovulation. The subjects

were instructed to do overnight fasting (10 hour) on the night before the experiment day. Five millilitres of venous blood were drawn between 8 a.m and 9 a.m during each phase of the menstrual cycle. Each sample was analyzed for serum calcium and serum magnesium levels.

Serum calcium level was measured by Photometric test for calcium; o-cresol-phthaleine complex one method. Serum magnesium level was measured by Photometric Colorimetric test for magnesium; Lipid clearing factor (LCF) method. Statistical analysis of the three sets of data (follicular, ovulatory and luteal phases) for each analysis was carried out by ANOVA Test. Differences were considered significant when $P < 0.05$.

Results

The mean ± SD age of the subjects was 27.1 ± 5.1 years. The duration of the menstrual cycle varied from 26 to 33 days with a mean ± SD of 29 ± 0.9 days. The duration of the menstrual phase varied from 2 to 7 days and mean ± SD was 3.6 ± 1.1 days. The basal body temperature (mean ± SD) was 98 ± 0.25˚F in the follicular phase and 98.7 ± 0.3˚F in the luteal phase. The average rise in the basal body temperature was 0.7˚F (0.4 - 1.1˚F) during the luteal phase. This indicates that all women participating in this study had ovulation during study period i.e., 2 successive menstrual cycles.

Values of serum calcium levels, serum magnesium levels and calcium:magnesium ratio in different phases of the menstrual cycle are shown in Table 1. The serum calcium level was 9.5 ± 0.3 mg/dL in the follicular phase, 9.2 ± 0.25 mg/dL in the ovulatory phase and 9.05 ± 0.2 mg/dL in the luteal phase. In all three phases of the menstrual cycle, serum calcium levels were within the normal range. Upon analysis by ANOVA (Bonferroni) test, serum calcium levels were found to be significantly higher during the follicular phase than in the other two phases. It progressively and significantly decreased from the follicular phase to the ovulatory phase ($P < 0.01$) and from the ovulatory phase to the luteal phase ($P < 0.01$) (Figure 1A).

Table 1. Serum calcium levels, serum magnesium levels and calcium magnesium ratio in different phases of the menstrual cycle

	Mean ± SD		
	Follicular Phase	**Ovulatory Phase**	**Luteal Phase**
Serum calcium levels	9.5 ± 0.3 mg/dL	9.2 ± 0.25 mg/dL*	9.05 ± 0.2 mg/dL***
Serum magnesium levels	2.3 ± 0.1 mg/dL	2.15 ± 0.15 mg/dL*	2.0 ± 0.25 mg/dL**
Calcium:Magnesium ratio	4.15 ± 0.25	4.3 ± 0.35*	4.55 ± 0.5***

* indicates significant difference between the follicular and ovulatory phase ($P < 0.01$)

** indicates significant difference between the ovulatory and luteal phase ($P < 0.05$)

*** indicates significant difference between the ovulatory and luteal phase ($P < 0.01$)

The serum magnesium level was 2.3 ± 0.1 mg/dL in the follicular phase, 2.15 ± 0.15 mg/dL in the ovulatory phase and 2.0 ± 0.25 mg/dL in the luteal phase. In all three phases of the menstrual cycle, serum magnesium levels were within the normal range. It progressively and significantly decreased from the follicular phase to the ovulatory phase ($P < 0.01$) and from the ovulatory phase to the luteal phase ($P < 0.05$) (Figure 1B).

The calcium : magnesium ratio was 4.15 ± 0.25 in the follicular phase, 4.3 ± 0.35 in the ovulatory phase and 4.55 ± 0.5 in the luteal phase. The ratio was the lowest in the follicular phase and the highest in the luteal phase. It progressively and significantly increased from the follicular phase to the ovulatory phase ($P < 0.01$) and from the ovulatory phase to the luteal phase ($P < 0.01$) (Figure 1C).

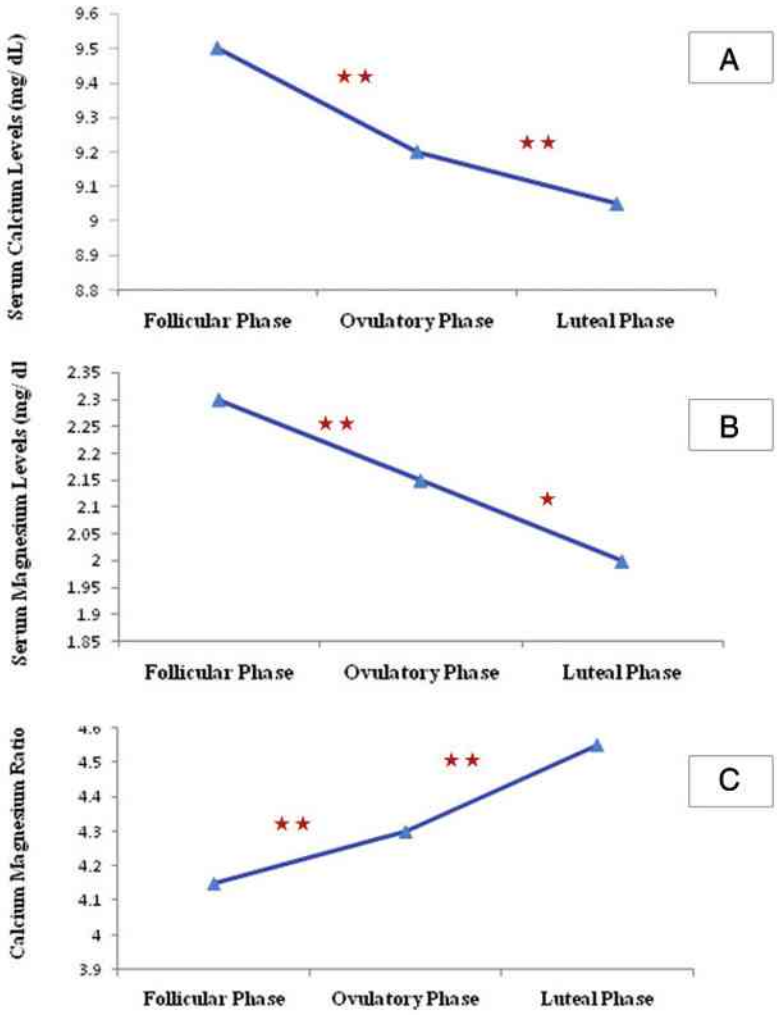

Figure 1. Serum calcium levels (Panel A), serum magnesium levels (Panel B) and calcium magnesium ratio (Panel C) in different phases of the menstrual cycle
* indicates significant difference ($P < 0.05$)
** indicates significant difference ($P < 0.01$)

Discussion

The menstrual cycle is unique to females and it results from a complex interaction between the hypothalamus, the anterior pituitary gland, the ovaries and the uterus. At puberty, the anterior pituitary, driven by pulsatile secretion of GnRH from the hypothalamus, begins to secrete FSH and LH which in turn influence estrogen and progesterone secretions from the ovaries. Over the course of the menstrual cycle, estrogen and progesterone are responsible for the changes that occur in the endometrium, cervix, and vagina. The fluctuations in circulating estrogen and progesterone levels during the ovarian cycle induce profound changes in the physical and affective nature of the menstruating women.

According to the physiology of the normal menstrual cycle, estrogen level during the early follicular phase is low. With the growth of the ovarian follicles, estrogen secretion increases. Near the midcycle (36 - 48 hour before ovulation), increased estrogen secretion from the rapidly growing follicles and synergetic action of FSH and LH cause rapidly rising estrogen level which in turn induces LH surge. Estrogen peak is a short period about 36 hours and then estrogen level falls rapidly. The estrogen level gradually rises again over the luteal phase. During the menstrual cycle, the estrogen level in the follicular phase is lower than that in the ovulatory phase and in the luteal phase. There is rapidly rising estrogen level over a short period (about 36 hours) in the ovulatory phase, and the gradually rising estrogen level over a longer period in the luteal phase[10].

In the present study, the serum calcium concentrations in all three phases of the menstrual cycle were within normal range (8.5 to 10.3 mg/dL or 2.1 - 2.6 mmol/L)[11]. The serum calcium level was peak in the follicular phase and lowest in the luteal phase. This finding agreed with the reports of the previous studies, such as Thys-Jacob *et al* in 2007[12] and Dullo and Vedi in 2008[13]. The finding of the present study differed from previous study of Pandya *et al* in 1995[14] who reported that serum calcium level was highest in the ovulatory phase. However, the lowest serum calcium level in the luteal phase was similar to the present study. Considering the findings of all these studies including present study, different studies showed different pattern of serum calcium fluctuation during different phase of the menstrual cycle. During the menstrual cycle, the estrogen level in the follicular phase is lower than those in the ovulatory phase and the luteal phase[10]. The higher levels of estrogen during ovulatory and luteal phases compared to during the follicular phase could be responsible for these low serum calcium levels. Reportedly, estrogen inhibits bone resorption and antagonizes the effect of PTH on bone and so estrogen tends to lower serum calcium level[15]. Heaney in 1976[16] noted that serum calcium level was increased in postmenopausal women and Thys-Jacob and Alvir in 1995[17] demonstrated that the serum calcium level significantly decline at midcycle coninciding with increase in estrogen level. Our results are in agreement with these reports.

Normal range of serum magnesium level is 1.8 to 3.0 mg/dL (0.75 - 1.25 mmol/L)[11]. In the present study, serum magnesium levels in all three phases of the menstrual cycle were within normal range. The serum magnesium levels progressively and significantly decreased from the follicular phase to the ovulatory phase and then from the ovulatory phase to the luteal phase. Muneyyirci-Delale *et al* in 1999 reported that serum levels of ionized and total magnesium were inversely correlated with the estrogen concentration[18]. The raised estrogen levels during the ovulatory phase could possibly be acting on the parathyroid gland, due to which serum magnesium levels dropped as reported by Pitkin *et al* in 1978[19]. Estrogen is known to increase the utilization of magnesium by the body. It has been reported that magnesium ions and oxidative enzymes are needed for carbohydrate utilization which increases significantly during the luteal phase[20].

In this study, the percent fall of serum calcium from the follicular to the luteal phase is 4.7% and that of serum magnesium was 13%. Magnesium drop was more pronounced than that of calcium during the luteal phase. Therefore, calcium:magnesium ratio increased progressively from the follicular phase to the luteal phase. The highest calcium:magnesium ratio in the luteal phase as compared to the other two phases could be due to estrogen as reported previously[21]. As a general rule, the human body structure need calcium with relative more magnesium. The ratio of calcium to magnesium is vital for cell membranes and the blood-brain barrier. There was a relative deficiency of magnesium compared to calcium in acute or chronic, seriously ill patients. Accordingly, increased calcium:magnesium ratio during the luteal phase in this study would be responsible for appearance of the menstruation related symptoms in the luteal phase.

Conclusion

Women of reproductive age demonstrate cyclical changes of calcium and magnesium levels and calcium:magnesium ratio in their serum. During the luteal phase, there was less decrease in calcium with relatively more decrease in magnesium and so calcium:magnesium ratio increased. The changes in serum concentrations of these important physiologically active cations, in the range at which they occur, can affect such entities as the vasculature, synaptic transmission, and excitation-secretion coupling and thus can produce the well-known premenstrual syndromes (PMS) during the luteal phase in menstruating women. This study enabled us to reduce the menstruating related symptoms with the use of calcium supplementation containing relatively more magnesium, and alert us to measure serum calcium and magnesium levels as well as calcium:magnesium ratio in females who suffered from PMS.

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