ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2007; 27 (1): 51-58
1173-2563/07/0001-0051/$44.95/0

© 2007 Adis Data Information BV. All rights reserved.

Pilot Study of the Efficacy and Safety of a Modified-Release Magnesium 250mg Tablet (Sincromag®) for the Treatment of Premenstrual Syndrome

S. Quaranta,[1] *M.A. Buscaglia*,[1] *M.G. Meroni*,[2] *E. Colombo*[2] and *S. Cella*[3]

1 Unità Operativa Ostetricia e Ginecologia, Azienda Ospedaliera Ospedale San Carlo Borromeo, Milan, Italy
2 Unità Operativa Ostetricia e Ginecologia, Azienda Ospedaliera di Busto Arsizio, Varese, Italy
3 Facoltà di Medicina e Chirurgia Università di Milano, Presso Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica, Milan, Italy

Abstract

Background: Magnesium deficiency has been implicated as a possible contributing factor to some symptoms of premenstrual syndrome (PMS) and several studies have reported a lower intracellular magnesium concentration in women with PMS. Thus, it has been suggested that magnesium supplementation may improve certain symptoms in women with PMS.

Objective: This open-label study assessed the efficacy and safety of a patented modified-release magnesium 250mg tablet for improving symptoms in women affected by PMS.

Methods: After a 3-month observational period, women aged 18–45 years with a regular menstrual cycle (from 25–35 days) who were affected by PMS (determined by a score of ≥25 points on a PMS questionnaire) [n = 41] were given the modified-release magnesium tablet over three menstrual cycles, beginning 20 days after the start of their last menstrual period and continuing until the start of their next menstrual period.

Results: PMS symptoms improved during magnesium treatment. After 3 months, the mean total PMS score (primary endpoint), as assessed by the investigator using Moos' Modified Menstrual Distress Questionnaire, was significantly lower than before therapy ($p < 0.0001$). During the same period, the mean PMS scores, as recorded in patients' diaries (secondary efficacy variables), also showed significant improvements ($p < 0.0001$ for all subscales). The relative decreases in total PMS scores, as assessed by investigator and patient, were 35.1% and 33.5%, respectively. The magnesium tablet was well tolerated, with vertigo the only treatment-related adverse event reported (one patient).

Conclusions: We concluded that modified-release magnesium was effective in reducing premenstrual symptoms in women with PMS in this preliminary study.

Introduction

Premenstrual syndrome (PMS) is characterised by emotional, behavioural and physical symptoms that occur in the luteal phase before the menstrual period. The symptoms vary in severity and may impair women's quality of life. A number of diagnostic criteria, including those of the International Classification of Diseases (10th Edition),[1] the American College of Obstetricians and Gynecologists[2] and the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition),[3] are currently used. However, the diagnostic criteria for PMS remain inconclusive and these published criteria are not widely accepted.[4]

The estimated prevalence of PMS varies considerably, ranging from 20% to 80%.[5-7] The prevalence of premenstrual dysphoric disorder (PMDD), a severe form of PMS, is estimated at 2–9%.[8]

PMS symptoms are often classified into subgroups of symptoms based on a common physical alteration. One of the proposed classifications[9] separates the symptoms into four subgroups: PMS-A (anxiety), PMS-C (craving), PMS-D (depression), and PMS-H (hydration) [table I]. Many authors have linked the symptoms detailed in table I with changes in hormonal levels. It has been documented that higher estrogen levels may induce PMS symptoms related to mood alterations.[10-12] Higher levels of luteinising hormone (LH), particularly in the evening, can be correlated to stronger symptoms.[13] Higher progesterone levels also appear to be related to PMS symptoms.[14,15] There is also evidence of a link between melatonin and dysphonic symptoms of PMS.[16-18]

Intracellular magnesium levels regulate several enzymatic reactions and the hypoactivity of magnesium has been involved in different pathological states such as PMS. There is a strict relationship between magnesium concentrations and gonadal hormone secretion and activity. In fact, serum magnesium levels, as well as gonadal steroid concentrations, have been shown to vary cyclically in women of reproductive age.[19] On the other hand, other authors have shown that only intracellular magnesium concentrations change during the menstrual cycle.[20] Magnesium ion concentrations also seem to be directly related to progesterone levels in men[21] and inversely related to estrogen levels in postmenopausal women.[22] Moreover, estrogen and progesterone therapy significantly decreased urinary magnesium excretion.[23] In women with PMS, along with the reported hormonal alterations, the amounts of magnesium in erythrocytes and leukocytes have been found to be lower than those of control women.[24] Taken together, these observations would confirm that in women with PMS, gonadal hormones may interfere with magnesium balance. Women with PMS also present an altered secretory profile of melatonin, a hormone likely involved in their premenstrual mood changes.[25-27] These chronobiological alterations may be secondary to a magnesium defect, since it has been demonstrated that a reduction in magnesium concentrations impairs the activity of the pineal gland.[28,29]

Higher levels of estradiol and LH during the luteal phase have been related to more severe PMS symptoms.[30] The levels of these, and of other related hormones, appear to follow a circadian rhythm with secretory peaks occurring during the late evening or the night.[31,32]

The patented modified-release magnesium tablet (Sincromag®, Zambon Group S.p.A.)[1] was designed to release ionised magnesium in a biphasic manner

Table I. Classification of premenstrual syndrome (PMS) symptoms according to Abraham[9]

PMS-A: anxiety	PMS-C: craving	PMS-D: depression	PMS-H: hydration
Nervous tension, mood swings, irritability, anxiety	Headache, craving for sweets, increased appetite, heart pounding, fatigue, dizziness or faintness	Depression, forgetfulness, crying, confusion, insomnia,	Weight gain, swelling of extremities, breast tenderness, abdominal bloating

1 The use of trade names is for product identification purposes only and does not imply endorsement.

© 2007 Adis Data Information BV. All rights reserved.

(pulsatile release). The first phase, known as the 'supplier release phase', consists of an initial greater release of magnesium. The second phase, or 'protective phase', is a smaller release of magnesium ions that occurs about 4–6 hours after the first release, intended to restore the intracellular physiological concentrations (data on file Zambon Group S.p.A.). The tablet should be taken in the evening so that the first magnesium release coincides approximately with secretory peaks of melatonin and LH. The second phase of release is intended to exert a protective effect against estrogen and prolactin peaks.

The aim of this study was to perform an initial evaluation of the efficacy and safety of 3 months' treatment with modified-release magnesium tablets for improving symptoms in women affected by PMS.

Methods

Patients

Women aged 18–45 years with a regular menstrual cycle (from 25 to 35 days) who were affected by PMS were eligible for enrolment in the study. Diagnosis of PMS was defined as reaching ≥25 points on the Moos' Modified Menstrual Distress Questionnaire (MMDQ)[33,34] at screening. Patients were included without regard to prior pregnancies.

Patients were excluded from the study for the following reasons: pregnancy or using oral contraceptives at the time of the screening visit; unstable metabolic and/or hormonal disorder; acute or chronic systemic diseases; severe cardiovascular, hepatic, haematological, renal, gastrointestinal or pulmonary diseases; a history or evidence of a major gynaecological disorder other than PMS (e.g. endometriosis or pelvic inflammatory disease); diagnosed psychiatric disorder; or active malignancy. Patients who had taken magnesium supplementation within the previous 3 months before the screening visit or those with a history of allergy and/or poor tolerability to the study product were also excluded.

Concomitant administration of drugs that could modify the plasma level of magnesium (e.g. calcium channel antagonists, diuretics, cholestyramine, pancreatic lipase inhibitors, other drugs that affect intestinal absorption, or the continuous use of laxatives) or that acted on the CNS were not permitted. Patients who had taken drugs or hormones over the previous 2 months that could affect the activity of different endocrine axes were also excluded. Other exclusion criteria were antihypertensive treatment, a history of alcohol or drug abuse, and concomitant participation in another clinical trial.

All subjects provided written informed consent before admission into the study. The study was performed in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice, and was approved by the ethics committees of the two participating centres.

Study Design

This was an open-label trial carried out at two centres in Italy from 2004 to 2006 to evaluate the efficacy and safety of a modified-release magnesium 250mg tablet for the prevention of PMS symptoms. The study was divided into two phases: a 3-month observation period followed by a 3-month treatment period. During the treatment period, patients were instructed to take one magnesium tablet once daily in the evening, beginning 20 days after the start of the last menstruation (the third menstrual cycle after the screening visit) and continuing until the start of the next menstrual period.

Patients made three visits to the investigator: visit 1 was a screening visit before the 3-month observation period; visit 2 was a control visit that took place three menstrual cycles after the screening visit and before the start of treatment; and visit 3 occurred after patients had experienced three menstrual cycles while on treatment.

At all visits, patients underwent a physical examination, and the investigator assessed the patients' status with regard to PMS using the MMDQ. Gynaecological examinations were also carried out at visits 1 and 3. During the observational period and the treatment period, patients were required to complete a diary of symptoms relating to PMS after each menstrual cycle according to the MMDQ.

© 2007 Adis Data Information BV. All rights reserved.

Compliance was assessed by tablet count at the end of the treatment period relative to the number of tablets that should have been returned. Concomitant treatments (treatments taken within the 12 weeks prior to study entry or during the study) were recorded by the investigator in the patient records.

Efficacy Measures

The primary endpoint of the study was improvement in PMS symptoms as assessed by the investigator using the MMDQ. Symptoms evaluated were nervous tension, mood swings, irritability, anxiety, weight gain, swelling of extremities, breast tenderness, abdominal bloating, headaches, craving for sweets, increased appetite, heart pounding, fatigue, dizziness, depression, forgetfulness, easy crying, confusion and insomnia. Each symptom was graded as follows: 0 = none, 1 = mild, 2 = moderate or 3 = severe, and the total score was calculated as the sum of the single scores obtained for each symptom.

The secondary endpoint was the improvement in PMS symptoms according to a monthly diary in which women were requested to report their symptoms using the MMDQ after each menstrual cycle. The symptoms were divided into four subscales as detailed in table I. Each symptom was graded as follows: 0 = none, 1 = mild, 2 = moderate or 3 = severe, and the sum of single scores within each subscale was calculated.

Safety Measures

Safety was monitored by recording all adverse events reported by the subjects to the investigator at each study visit, by performing physical examinations at each visit, and by conducting a gynaecological examination at screening and at the final visit.

Statistical Analysis

Efficacy analyses were performed on the full analysis set, which consisted of all patients with a complete evaluable efficacy questionnaire assessed by the investigator (intention to treat [ITT]). The scores obtained at each visit were evaluated using the General Linear Model for repeated measurements and SAS (Statistical Analysis Software) to determine differences (plus 95% CIs) between screening (visit 1) and post-treatment (visit 3), and between visit 1 and visit 2.

The safety population included all patients who received at least one dose of the study medication.

Results

Patient Population

Of the 45 patients enrolled, 41 entered the study and received at least one dose of the study treatment. In addition to the four enrolled patients who did not receive treatment, one patient had no efficacy evaluation and was excluded from the analysis set. Thus, the ITT population consisted of 40 patients. Three other patients did not complete the study according to the protocol because of lack of compliance/poor compliance, withdrawal of consent or other protocol violation. Overall, 38 patients completed the study according to the protocol. The demographic characteristics of patients who were treated are shown in table II. All patients except two (one Colombian and one Egyptian) were Caucasian.

Compliance, as assessed by a tablet count at the end of the treatment period, was 102.8% (suggesting patients on average consumed slightly more tablets than recommended), and the mean duration of treatment over the three cycles was 27.9 ± 9.9 days.

Efficacy

Primary Efficacy Variable

The mean total scores for the PMS symptoms at each visit are shown in table III. There was no significant difference between the baseline mean total score (at the screening visit) and the mean total score at visit 2 (after completion of the 3-month observation period).

At the end of the 3-month treatment phase, the mean total score from the PMS questionnaire was significantly lower than the baseline value (19.7 ± 7.6 vs 30.5 ± 4.5, respectively; $p < 0.0001$). This reduction was equivalent to a 35.1% relative decrease (improvement) in total score (table III).

© 2007 Adis Data Information BV. All rights reserved.

Table II. Demographic and baseline characteristics of patients who received magnesium treatment (n = 41)[a]

Age (y)	32.6 ± 8.0 (18–45)
Weight (kg)	57.5 ± 9.5 (42–95)
Height (cm)	162.6 ± 6.5 (145–176)
Length of menstrual cycle (days)	28.0 ± 1.8 (23–32)

a All data are mean ± SD (range).

Secondary Efficacy Variables

The mean total scores for PMS symptoms rated by the patients in their diaries are reported in table IV and the mean symptom scores for each of the PMS symptom subscales are shown in figure 1. The mean total scores for the three treatment cycles were 23.3 ± 10.6, 19.6 ± 7.8 and 17.9 ± 7.3, respectively, compared with a mean total score of 31.8 ± 6.4 at the first observation phase and 31.3 ± 8.4 at the second evaluation, immediately before treatment (table IV). This corresponded to a 43.5% relative decrease in total score at the end of the treatment period ($p < 0.0001$).

Over the 3-month observation period, the mean scores for PMS-A, PMS-H, PMS-C and PMS-D showed little variation between menstrual cycles. During treatment, PMS-A, PMS-H, PMS-C and PMS-D were significantly decreased in comparison with baseline at each cycle (all $p < 0.0001$). The total score and the subscale scores appeared to be decreased over each cycle during the treatment phase (figure 1).

Safety

The safety analysis included all 41 patients who received the study treatment.

During the study, 18 patients experienced a total of 72 adverse events. The only adverse event considered to be possibly related to treatment was vertigo, which occurred in one patient during the treatment phase.

No serious adverse events occurred during the study, and no patients discontinued the study because of adverse events.

There were no clinically significant changes in comparison with baseline for vital signs, systolic or diastolic blood pressure or heart rate, and no worsening of physical examination signs during the study. One patient had symptoms of disease (possible endometrioma) at the final gynaecological visit, and only one patient refused to attend for the final gynaecological visit.

Discussion

In this study we demonstrated that, in patients with PMS, administration of magnesium 250mg tablets with a patented modified-release formulation over three menstrual cycles significantly improved both investigator- and patient-assessed PMS symptom scores. The modified-release magnesium tablet was well tolerated.

The relative decrease in total PMS scores was 35.1%, as assessed by the investigator at the end of treatment, and 25.3%, 37.4% and 42.9%, respectively, during each of the three treatment cycles, as assessed by patient diaries.

With regard to the patients' subjective evaluation of symptom scores obtained in the different domains, a marked improvement with respect to baseline was observed during the three subsequent cy-

Table III. Primary efficacy variable: mean total scores for the premenstrual syndrome questionnaire[a] as assessed by the investigator

	Visit 1 (baseline)	Visit 2 (pretreatment)	Visit 3 (end of treatment)
No. of patients	40	40	40
Mean total score ± SD	30.5 ± 4.6	31.7 ± 5.9	19.7 ± 7.6
Absolute change		1.2	−10.8
Relative change (%)		4.5	−35.1
95% CI[b]			−13.236, −8.414
p-Value			<0.0001

a Moos' Modified Menstrual Distress Questionnaire.[33]

b For absolute change value at visit 3.

© 2007 Adis Data Information BV. All rights reserved.

Table IV. Secondary efficacy variable: mean total scores for premenstrual syndrome-related symptoms[a] from patient diaries

	Cycles of observation			Cycles of treatment		
	1	2	3	1	2	3
No. of patients	39	39	39	39	39	38
Mean total score ± SD	31.8 ± 6.4	30.2 ± 7.7	31.3 ± 8.4	23.3 ± 10.6	19.6 ± 7.8	17.9 ± 7.3
Absolute change[b]				−7.9	−11.7	−13.4
Relative change (%)				−25.3	−37.4	−42.9
95% CI[c]				−11.528, −4.715	−15.395, −8.579	−16.545, −10.190
p-Value				<0.0001	<0.0001	<0.0001

a Moos' Modified Menstrual Distress Questionnaire divided into four subscales.[9,33]

b Difference vs third observational value.

c For absolute change values at treatment cycles 1, 2 and 3.

cles when treatment was administered, apart from in the PMS-H field, which showed a smaller improvement. The fact that magnesium was more effective on the 'central' dysphoric components of PMS (PMS-A, PMS-C and PMS-D) than on the 'peripheral' component (PMS-H) probably indicates that magnesium acts primarily by normalising the actions of different hormones (mainly progesterone) on the CNS. Progesterone induces 'depressive' symptoms[14,15] and, therefore, a hypersensitivity to its central effects could be involved in PMS. This study supports this theory, showing significant improvements in PMS-D symptoms with magnesium treatment. This effect of magnesium on the CNS also provides further proof of the usefulness of a formulation that biphasically releases the ion, coinciding with the peaks of different hormones probably involved in PMS pathogenesis.

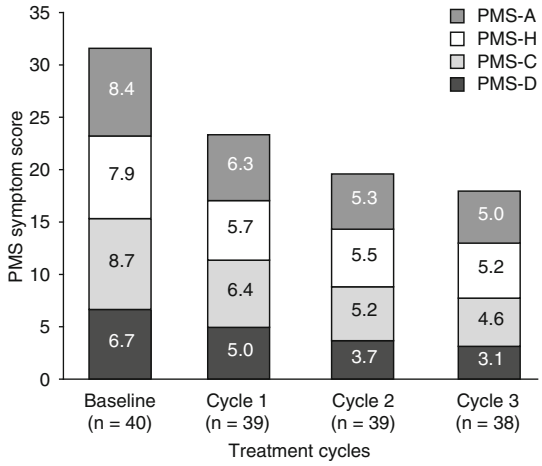

Fig. 1. Premenstrual syndrome (PMS)-related symptom scores during treatment with a modified-release magnesium 250mg tablet over three menstrual cycles, as recorded in patient diaries. Symptoms were divided into four subscales: **PMS-A** = anxiety (nervous tension, mood swings, irritability, anxiety); **PMS-H** = hydration (sensation of weight gain, swelling of extremities, breast tenderness, abdominal bloating); **PMS-C** = craving (headache, craving for sweets, increased appetite, heart pounding, fatigue, dizziness or faintness); and **PMS-D** = depression (depression, forgetfulness, easy crying, confusion, insomnia). Each symptom was graded as follows: 0 = none, 1 = mild, 2 = moderate or 3 = severe, and the sum of symptom scores within each subscale was calculated. Subscale scores were significantly decreased from baseline during treatment cycles 2 and 3 ($p < 0.0001$ for all subscales).

This study was limited by the small sample size, and as it was intended to provide only an initial assessment of the efficacy and safety of the new magnesium tablet, it cannot therefore be used to draw definitive conclusions about the importance of magnesium deficiency in PMS. Because the placebo response in PMS trials may be fairly high, with as many as 20% of patients achieving a sustained ≥50% improvement in PMS symptoms,[35] the absence of a placebo control in this study may have resulted in better responses than might have been seen in a placebo-controlled trial. Also, the nature of PMS symptoms makes for difficulties assessing many of these symptoms objectively.

Other trials have also reported improvements in PMS symptoms with magnesium supplementation. Interestingly, the types of symptoms that improved were not the same across all studies. One study reported an improvement in PMS-H (particularly fluid retention) with thrice-daily administration of magnesium,[36] while another study reported a significant reduction in anxiety-related premenstrual

© 2007 Adis Data Information BV. All rights reserved.

symptoms with a combination of magnesium and pyridoxine (vitamin B_6).[37] Although subscales of PMS symptoms were assessed only as a secondary efficacy endpoint in the current study, there appeared to be an overall improvement in all PMS subscales.

The modified-release magnesium tablet was formulated in order to release magnesium ions coincident with the circadian rhythms of hormones that may be related to PMS symptoms. In particular, melatonin peaks around 2am and LH peaks at 10pm–2am,[38,39] while estradiol and prolactin peak in the early morning.[32,38,39] When taken in the evening, the modified-release tablet will provide two phases of magnesium release (data on file, Zambon Group S.p.A.): the first is intended to coincide with the melatonin peak (to enhance the action of melatonin in PMS) and the LH peak (to enhance the functioning of LH). The second release of magnesium around 4–6 hours later coincides with peaks of estradiol and prolactin and may prevent magnesium intracellular reduction and the dopamine intracellular depletion,[40] and thus preventing the prolactin increase.[41]

It is important to note that intracellular magnesium deficiency has not been consistently demonstrated across all studies in women with PMS.[42] Furthermore, treatment with a single dose of intravenous magnesium in the study by Khine et al.[42] showed no benefits in patients' mood relative to placebo. On the basis of these inconclusive findings, it is now important to conduct randomised, placebo-controlled trials to further explore this issue.

Conclusion

While the role of magnesium deficiency in PMS is still not well established and the limited dimensions of this study do not allow definitive conclusions to be drawn, the results of this study represent new evidence supporting the utility of magnesium supplementation in the treatment of PMS and suggest that magnesium 250mg, when released in conjunction with circadian hormone levels, may improve symptoms for women with PMS. Therefore, this patented modified-release formulation, which takes into consideration daily changes in hormone levels in women, can be regarded as a new modality for the administration of magnesium and opens up new scientific areas of interest relating to prevention of depletion of intracellular magnesium in women with PMS.

Acknowledgements

The publication of this manuscript was supported by an educational grant from Zambon Group S.p.A. The editorial assistance of Marit Moen, Wolters Kluwer Health Medical Communications, is gratefully acknowledged.

The authors have no potential conflicts of interest that are directly relevant to the contents of this study.

References

1. International Statistical Classification of Diseases and Health Related Problems – ICD-1 Edition. WHO 1987
2. American College of Obstetricians and Gynecologists (ACOG). Premenstrual syndrome (ACOG practice bulletin no. 15). Washington (DC): ACOG; 2000
3. Diagnostic and Statistical manual of Mental Disorders, Fourth Edition. American Psychiatric Association, 1994
4. Halbreich U. The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder: clinical procedures and research perspectives. Gynecol Endocrinol 2004 Dec; 19 (6): 320-34
5. Dalton K. What is PMS? J Roy Coll Gen Pract 1982; 32: 717-23
6. Johnson SR. The epidemiology and social impact of premenstrual symptoms. Clin Obstet Gynecol 1987; 30; 367-6
7. Winer SA, Rapkin AJ. Premenstrual disorders: prevalence, etiology and impact. J Reprod Med 2006; 51; 339-47
8. Freeman EW, Sondheimer SJ. Premenstrual dysphoric disorder: recognition and treatment. Prim Care Companion J Clin Psychiatry 2003 Feb; 5 (1): 30-9
9. Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndromes. J Reprod Med 1983 Jul; 28 (7): 446-64
10. Halbreich U. Gonadal hormones and antihormones serotonin and mood. Psychopharmacol Bull 1990; 26: 291-5
11. Halbreich U, Tworek H. Altered serotonergic activity in women with dysphoric premenstrual syndromes. Int J Psychiatry Med 1993; 23: 1-27
12. Genazzani AR, Lucchesi A, Stomati M, et al. Effects of sex steroid hormones on the neuroendocrine system. Eur J Contracept Reprod Health Care 1997; 2: 63-9
13. Seippel L, Backstrom T. Luteal-phase estradiol relates to symptom severity in patient with premenstrual syndrome. J Clin Endocrinol Metab 1998; 83: 1988-92
14. Magos AL, Brewster E, Singh R, et al. The effect of norethisterone in postmenopausal women on estrogen therapy: a model for the premenstrual syndrome. Br J Obstect Gynecol 1986; 93: 1290-6
15. Bjorn I, Bixo M, Nojd KS, et al. Negative mood changes during hormone replacement therapy: a comparison between two progestogens. Am J Obstet Gynecol 2000; 183: 1419-26

© 2007 Adis Data Information BV. All rights reserved.

16. Parry BL, Berga SL, Kripke DF, et al. Altered waveform of plasma nocturnal melatonin secretion in premenstrual depression. Arch Gen Psychiatry 1990; 47: 1139-46

17. Parry BL, Newton RP. Chronobiological basis of female-specific mood disorders. Neuropsychopharmacology 2001; 25 (Suppl. 5): S102-8

18. Pacchierotti C, Iapichino S, Bossini L, et al. Melatonin in psychiatric disorders: a review on the melatonin involvement in psychiatry. Front Neuroendocrinol 2001; 22: 18-32

19. Deuster PA, Dolev E, Bernier LL. Magnesium and zinc status during the menstrual cycle. Am J Obstet Gynecol 1987; 157: 964-68

20. Facchinetti F, Borella P, Valentini M, et al. Premenstrual increase of intracellular magnesium levels in women with ovulatory, asymptomatic menstrual cycles. Gynecol Endocrinol 1988; 2: 249-56

21. Muneyyirci-Delale O, Dalloul M, Nacharaju V L, et al. Serum ionized magnesium and calcium and sex hormones in healthy young men: importance of serum progesterone level. Fertility Sterility 1999; 72: 817-22

22. Muneyyirci-Delale O, Nacharaju VL, Dalloul M, et al. Serum ionized magnesium and calcium in women after menopause: inverse relation of estrogen with ionized magnesium. Fertility Sterility 1999; 71: 869-72

23. Schlemmer A, Podenphant J, Riis BJ, et al. Urinary magnesium in early postmenopausal women: influence of hormone therapy on calcium. Magnesium Trace Elements 1991-1992; 10: 34-9

24. Rosenstein DL, Elin RJ, Hosseini JM, et al. Magnesium measures across the menstrual cycle in premenstrual syndrome. Biological Psychiatry 1994; 35: 557-61

25. Parry BL, Berga SL, Kripke DF, et al. Altered waveform of plasma nocturnal melatonin secretion in premenstrual depression. Arch Gen Psychiatry 1990; 47: 1139-46

26. Parry BL, Udell C, Elliott JA, et al. Blunted phase-shift responses to morning bright light in premenstrual dysphoric disorder. J Biol Rhythms 1997; 12: 443-56

27. Parry BL, Berga SL, Mostofi N, et al. Plasma melatonin circadian rhythms during the menstrual cycle and after light therapy in premenstrual dysphoric disorder and normal control subjects. J Biol Rhythms 1997; 12: 47-64

28. Durlach J, Pages N, Bac P, et al. Chronopathological forms of magnesium depletion with hypofunction or with hyperfunction of the biological clock. Magnes Res 2000; 15: 263-8

29. Durlach J, Pages N, Bac P, et al. Biorhythms and possible central regulation of magnesium status, phototherapy, darkness therapy and chronopathological forms of magnesium depletion. Agnes Res 2002; 15: 49-66

30. Seippel L, Backstrom T. Luteal-phase estradiol relates to symptom severity in patients with premenstrual syndrome. J Clin Endocrinol Metab 1998 Jun; 83 (6): 1988-92

31. Licinio J, Negrao AB, Mantzoros C, et al. Synchronicity of frequently sampled, 24-h concentrations of circulating leptin, luteinizing hormone, and estradiol in healthy women. Proc Natl Acad Sci U S A 1998 Mar 3; 95 (5): 2541-6

32. Norjavaara E, Ankarberg C, Albertsson-Wikland K. Diurnal rhythm of 17 beta-estradiol secretion throughout pubertal development in healthy girls: evaluation by a sensitive radioimmunoassay. J Clin Endocrinol Metab 1996 Nov; 81 (11): 4095-102

33. Moos RH. The development of a menstrual distress questionnaire. Psychosom Med 1968 Nov-Dec; 30 (6): 853-67

34. Ross C, Coleman G, Stojanovska C. Factor structure of the modified Moos Menstrual Distress Questionnaire: assessment of prospectively reported follicular, menstrual and premenstrual symptomatology. J Psychosom Obstet Gynaecol 2003 Sep; 24 (3): 163-74

35. Freeman EW, Rickels K. Characteristics of placebo responses in medical treatment of premenstrual syndrome. Am J Psychiatry 1999 Sep; 156 (9): 1403-8

36. Walker AF, De Souza MC, Vickers MF, et al. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. J Womens Health 1998 Nov; 7 (9): 1157-65

37. De Souza MC, Walker AF, Robinson PA, et al. A synergistic effect of a daily supplement for 1 month of 200mg magnesium plus 50mg vitamin B6 for the relief of anxiety-related premenstrual symptoms: a randomized, double-blind, crossover study. J Womens Health Gend Based Med 2000 Mar; 9 (2): 131-9

38. Webley GE, Lenton EA. The temporal relationship between melatonin and prolactin in women. Fertil Steril 1987 Aug; 48 (2): 218-22

39. Mitamura R, Yano K, Suzuki N, et al. Diurnal rhythms of luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol secretion before the onset of female puberty in short children. J Clin Endocrinol Metab 2000 Mar; 85 (3): 1074-80

40. Barbeau A, Rojo-Ortea JM, Brecht HM, et al. Deficience en magnesium et dopamine cerebrale. In: Durlack J. editor. First International Symposium on Magnesium Deficit in Human Pathology. Paris: F Vittel, 1973; 149-52

41. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin inhibitor. Endocrine Reviews 2001; 22 (6): 724-63

42. Khine K, Rosenstein DL, Elin RJ, et al. Magnesium (Mg) retention and mood effects after intravenous Mg infusion in premenstrual dysphoric disorder. Biol Psychiatry. Epub 2005 Sep 28 2006 Feb 15; 59 (4): 327-33

Correspondence: Dr *S. Cella*, Facoltà di Medicina e Chirurgia Università di Milano, Presso Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica, Via Vanvitelli, 32, Italy.
E-mail: silvano.cella@unimi.it

© 2007 Adis Data Information BV. All rights reserved.