The Journal of Obstetrics and Gynaecology

Taylor & Francis
Taylor & Francis Group

Journal of Obstetrics and Gynaecology

ISSN: 0144-3615 (Print) 1364-6893 (Online) Journal homepage: http://www.tandfonline.com/loi/ijog20

Menstrual disorders and premenstrual symptoms in adolescents: prevalence and relationship to serum calcium and vitamin D concentrations

Afsane Bahrami, Hamidreza Bahrami-Taghanaki, Mozhgan Afkhamizadeh, Amir Avan, Zahra Mazloum Khorasani, Habibollah Esmaeili, Bahareh Amin, Samine Jazebi, Delaram Kamali, Gordon A. Ferns, Hamid Reza Sadeghnia & Majid Ghayour-Mobarhan

To cite this article: Afsane Bahrami, Hamidreza Bahrami-Taghanaki, Mozhgan Afkhamizadeh, Amir Avan, Zahra Mazloum Khorasani, Habibollah Esmaeili, Bahareh Amin, Samine Jazebi, Delaram Kamali, Gordon A. Ferns, Hamid Reza Sadeghnia & Majid Ghayour-Mobarhan (2018): Menstrual disorders and premenstrual symptoms in adolescents: prevalence and relationship to serum calcium and vitamin D concentrations, Journal of Obstetrics and Gynaecology, DOI: 10.1080/01443615.2018.1434764

To link to this article: https://doi.org/10.1080/01443615.2018.1434764

Published online: 21 Mar 2018.

JOURNAL OF OBSTETRICS AND GYNAECOLOGY, 2018
https://doi.org/10.1080/01443615.2018.1434764

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Menstrual disorders and premenstrual symptoms in adolescents: prevalence and relationship to serum calcium and vitamin D concentrations

Afsane Bahrami[a,b]*, Hamidreza Bahrami-Taghanaki[c]*, Mozhgan Afkhamizadeh[d]*, Amir Avan[e]*, Zahra Mazloum Khorasani[f], Habibollah Esmaeili[g], Bahareh Amin[h], Samine Jazebi[b], Delaram Kamali[i], Gordon A. Ferns[j], Hamid Reza Sadeghnia[k] and Majid Ghayour-Mobarhan[e]

[a]Department of Modern Sciences and Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [b]Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [c]Complementary and Chinese Medicine, Persian and Complementary Medicine Faculty, Mashhad University of Medical Sciences, Mashhad, Iran; [d]Department of Endocrinology, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran; [e]Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; [f]Endocrine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; [g]Department of Biostatistics and Epidemiology, School of Health, Management and Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; [h]Cellular and Molecular Research Center, Department of Physiology and Pharmacology, Sabzevar University of Medical Sciences, Sabzevar, Iran; [i]Nursing student, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran; [j]Division of Medical Education, Brighton and Sussex Medical School, Falmer, Sussex, Brighton, UK; [k]Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

There have been several studies evaluating the association between vitamin and mineral status and menstrual disturbance. In the present study, we aimed to assess the relationship between the menstrual bleeding pattern and premenstrual syndrome (PMS) symptoms with serum 25-hydroxyvitamin D, and calcium levels in adolescent girls. A cross-sectional study was carried out in 897 high school girls from northeastern Iran. The prevalence of hypocalcaemia, normal serum calcium and hypercalcaemia was 27.1, 59.8 and 13.1%, respectively. The menstrual flow of participants differed significantly between the calcium status groups ($p = .005$). There was no significant association between the symptoms of PMS, as assessed by the questionnaire and serum vitamin D status, or serum calcium concentrations, apart from the irritability. There appears to be an association between serum calcium, menstrual blood loss and irritability in adolescent girls.

IMPACT STATEMENT

- **What is already known on this subject?** Several studies have evaluated the association of vitamin and mineral status with menstrual disturbance, although these relationships are not consistent, specifically among calcium and vitamin D levels with a menstrual bleeding pattern.
- **What do the results of this study add?** In the present study, we investigated the correlation of menstrual bleeding patterns and PMS with calcium and vitamin D levels in a large population in adolescent girls. We found that the level of calcium was associated with the level of menstrual blood loss and irritability. However, no significant association was observed between the menstrual bleeding pattern or the PMS symptoms with a vitamin D status.
- **What are the implications of these findings for future clinical practise/research?** Further studies are required to assess the value of a calcium adequate intake or a calcium supplementation for the amelioration of PMS and a better understanding the role of calcium in PMS.

KEYWORDS
Adolescence; menstrual cycle; premenstrual syndrome; vitamin D; calcium

Introduction

Premenstrual symptoms, collectively often referred to as premenstrual syndrome (PMS), and as dysmenorrhoea, are common gynaecological disorders affecting the quality of life and performance of young women (Obeidat et al. 2012). PMS is described as a cluster of disorders recognised by psychological and physical symptoms that occur during the luteal phase of the menstrual cycle, that subside after the onset of menses, and are related with some degree of inter-cycle variation (Freeman 2003). Young women often avoid consulting a doctor about PMS, and consequently, it has a negative effect on their physical and psychological welfare (Hickey and Balen 2003).

There are several hypotheses about the aetiology of PMS, including the possibility that some women are sensitive to fluctuating hormone levels within the menstrual cycle

CONTACT Majid Ghayour-Mobarhan ghayourm@mums.ac.ir Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; Hamid Reza Sadeghnia SadeghniaHR@mums.ac.ir Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran
*These authors contributed equally as first authors.

(Halbreich et al. 2006), with an inadequate increase in progesterone levels during the early luteal phase being one (Halbreich 2003). Several treatments have been suggested for the PMS, although few have been demonstrated to be effective.

Previous studies have reported a potential role of vitamin and mineral status in the aetiology of PMS, and perhaps a putative mechanism for the treatment of menstrual problems (Proctor and Murphy 2001). It has been shown that the calcium levels inside and outside cells may have effects on neuromuscular junctions and the frequency of psychological symptoms of PMS. Irritability, agitation and mania have been reported in connection with low ionised calcium during the first phase of menses (Thys-Jacobs et al. 2007).

The potential role of calcium has been studied previously, and it has been reported that reduced calcium levels during ovulation are related to the luteal phase of the cycle (Thys-Jacobs and Alvir 1995; Bertone-Johnson et al. 2005). Serum vitamin D has also been shown to fluctuate during the menstrual cycle along with alterations in oestradiol at ovulation and across the luteal phase in several, but not all of the studies (Thys-Jacobs 2000).

The vitamin D receptor is present in the reproductive tissues (Evans et al. 2004; Lerchbaum and Obermayer-Pietsch 2012; Luk et al. 2012) and a low level of tissue vitamin D may be related to several disturbances of the reproductive system, such as early menarche (Luk et al. 2012) and uterine fibroids (Baird et al. 2013). It has been reported that vitamin D reduces the production of prostaglandins (Lasco et al. 2012). The promoter region of the gene encoding the anti-Müllerian hormone (AMH) contains a vitamin D response element, suggesting that vitamin D may regulate the expression of AMH (Malloy et al. 2009). AMH, in turn, regulates the follicular recruitment, which offers a mechanism for vitamin D to affect ovarian function and the regularity of the menstrual cycle (Luk et al. 2012).

Vitamin D deficiency is associated with infertility in rats and mice (Lerchbaum and Obermayer-Pietsch 2012). Knockout mice lacking the enzyme for producing the active form of vitamin D show hypogonadism, oestrus cycle disturbances, arrested follicular development, lengthy oestrous cycles, anovulation, and hypoplastic uteri (Panda et al. 2001; Dicken et al. 2012).

The results of previous studies assessing the association between PMS and vitamin D and calcium status have been inconsistent. Thys-Jacobs et al. reported no significant differences in 25(OH)D, and 1,25$(OH)_2$D between a woman with premenstrual dysphoric disorder (PMDD) and their control group (Thys-Jacobs et al. 2007). Vitamin D intake has been reported to be inversely related to the prevalence of PMS (Bertone-Johnson et al. 2010), although the serum 25(OH)D concentrations were not related to the risk of PMS (Bertone-Johnson et al. 2014). Because of the limited and inconsistent data assessing the relationship between serum calcium and vitamin D with the menstrual problems in young women, we aimed to explore the relationship between the menstrual bleeding patterns and PMS with calcium and vitamin D levels in the adolescent girls living in northeastern Iran.

Materials and methods

Participants and setting

A cross-sectional study was conducted among high school girls from the cities of Mashhad and Sabzevar in Iran, during January 2015, as described previously (Bahrami et al. 2017, 2018; Tabatabaeizadeh et al. 2017). Participants were recruited from different high schools in these two cities using a randomised clustering method. The target population included adolescent girls in these areas in the age group 12–18 years who had menarche for at least 1 year prior to their time of recruitment. Written consent was obtained from the students and their parents. Girls were excluded if they were experiencing symptoms of untreated depression, history of high blood pressure or dyslipidaemia, renal or liver disease, cancer, or bone disease such as osteomalacia, malabsorption, rheumatologic disease, thyroid disease, hyperparathyroidism, multiple sclerosis, type 1 or type 2 diabetes, polycystic ovaries; or were taking specific drugs including corticosteroids, anticonvulsants, anabolic steroids, propranolol, or cimetidine. Of all of the 988 eligible students, 897 completed all the requirements for the study. The study protocol was approved by the Mashhad University of Medical Sciences.

Biochemical assessments

Ten millilitres of venous blood was obtained from each participant after an overnight fast, irrespective of the phase of the girls' menstrual cycle. The blood samples were centrifuged and the sera were collected. Serum was assayed for serum 25-hydroxyvitamin D [25(OH)D], calcium and albumin concentrations. The vitamin D measurements were made using an electrochemiluminescence method (Roche, Basel, Switzerland) using Roche, Cobas, Germany kit and a vitamin D status was categorised according to serum levels of 25(OH)D (Nesby-O'Dell et al. 2002; Gordon et al. 2004; Misra et al. 2008; Kumar et al. 2009): vitamin D deficiency $\leq$15 ng/ml, and non-vitamin D deficiency >15 ng/ml.

The serum concentrations of calcium and albumin were assessed using Pars Azmoon kits (Tehran, Iran), in accordance with the instructions provided. Albumin-corrected calcium was calculated using the following formulae (Sava et al. 2005):

$$\text{Corrected total calcium } (\text{mg/dl}) : \Big([4 - \text{albumin } (\text{g/l})] \times 0.8\Big) + \text{total serum calcium } (\text{mg/dl})$$

$$\text{Corrected total calcium } (\text{mmol/l}) = \text{Corrected total calcium } (\text{mg/dl}) \times 0.25.$$

Albumin-corrected calcium status was categorised into three groups according to serum levels: hypocalcaemia $\leq$2.17 mmol/l, normal serum calcium 2.17–2.47 mmol/l and hypercalcaemia $\geq$2.47 mmol/l (Gøransson et al. 2005).

Evaluation of menstrual pattern and premenstrual syndrome

In this study, the girls completed a questionnaire comprising questions about their menstrual cycle and PMS.

The questionnaire was self-administered or, with the aid of an expert nurse. The menstrual pattern variables included in the questionnaire were: their age at menarche, the presence of dysmenorrhoea, the average days of bleeding (short bleeding times of <4 d, normal times of 4–6 d, long times of >6 d), the duration of their latest menstruation intervals (>21, 21–35, > 35 d), and self-reported blood loss per cycle (as little, moderate, and heavy).

The girls were also asked to answer 16 items that described the symptoms and signs of PMS: the physical symptoms (abdominal pain, backache, foot pain, vomiting, nausea, and diarrhoea), any psychological and behavioural symptoms (appetite changes, irritability, fatigue, palpitation, lack of energy, sleep pattern changes, depression and sadness, decrease of interest, loss of concentration, and tendency to cry easily) and the severity of each symptom. The girls who had at least two symptoms, one physical and one psychological symptom were considered as having PMS, while those with just one symptom or no symptoms were regarded as Non-PMS (Mortola et al. 1990). The pain severity was rated as mild, severe and very severe.

Measurement of covariates

The demographic and anthropometric information including age, height, weight and waist circumference were obtained in health centres, by a trained paramedic. Body mass index (BMI) was calculated as weight (kilograms) divided by height (metres) squared. The physical activity was evaluated through a validated questionnaire and classified as metabolic equivalents (METs) in hours/day (Delshad et al. 2015). To measure smoking exposure, we asked about time of exposure during a day.

Statistical analysis

IBM SPSS Statistics 18.0 for Windows (SPSS Inc., Chicago, IL) was used for all of the statistical analyses. The Kolmogorov–Smirnov test was used to examine a normal distribution of variables. The categorical variables were expressed as a number (percentage) and quantitative variables as the mean ± SD or median (interquartile range [IQR]), as suitable. The categorical data were compared using the χ^2 test. The Student's *t*-test or ANOVA were used, as appropriate, to compare quantitative variables. Followed by ANOVA, Tukey HSD *post hoc* tests were conducted. $p < .05$ was considered statistically significant. A logistic regression analysis was applied to calculate the risk of PMS according to the calcium and vitamin D levels and as continuous or a categorical variable.

Results

Descriptive characteristics of the study population

The demographics, anthropometric, biochemical and lifestyle data of the participants are summarised in Table 1. The ages of the participants ranged from 12 to 18 in years with a mean age of 14.72 (±1.5) years. The mean BMI was 21.45 ± 4.2 kg/m^2 and girls averaged 45.29 ± 3.4 MET-hours per day of physical activity. 20.6% of participants disclosed aspects of smoking exposure. 85.3% of all participants had a vitamin D deficiency and 27.1% had corrected serum calcium below the reference range and 13.1% of them had corrected serum calcium levels above the reference range.

The characteristics of the menstrual cycle including cycle length, duration of flow, and amount of flow are reported in Table 2. The mean age at menarche of our study population was 12.61 ± 1.1 years. The most frequently observed menstrual cycle length was 21–35 d, with the most common menstrual bleeding length being 4–7 d. PMS (47.3%) was a common menstrual cycle disorder among the subjects in this study. Of whom, 37.3% required analgesic medicine for relief of symptoms.

The most common physical symptom was an abdominal pain (657 girls, 73.2%) and backache (537 girls, 59.9%). The most prevalent psychological and behavioural symptoms were an increased tendency to cry easily (292 girls, 32.5%), and a loss of concentration (259 girls, 28.9%) (Tables 3 and 4).

Relationship between calcium levels, menstrual bleeding pattern and PMS

The mean albumin-corrected calcium level was 2.26 mmol/l (standard deviation: 0.2), with a median of 2.27 mmol/l (IQR: 2.16, 2.37 mmol/l). Two hundred and forty-three of the 897 girls (27.1%) had low corrected serum calcium, 536 (59.8%) had normal-corrected serum calcium level, and 118 (13.1%) had a high, corrected serum level of calcium.

No significant differences were found for BMI, height, weight, smoking exposure or physical activity between the

Table 1. Relationship of characteristics of participants to serum calcium and vitamin D concentrations.

	Serum Vitamin D			Corrected serum calcium			
Variable	Deficiency ≤15 ng/ml	Non-deficient >15 ng/ml	*p* value	Hypocalcaemia ≤2.17 mmol/l	Normal 2.17–2.47 mmol/l	Hypercalcaemia ≥2.47 mmol/l	*p* value
Number of subject	765 (85.3%)	132 (14.7%)		243 (27.1)	536 (59.8)	118 (13.1)	
Age (year)	14.63 ± 1.49	15.03 ± 1.51	.009[a]	14.62 ± 1.52	15.0 ± 1.42	14.25 ± 1.32	<.001[c,d]
BMI (kg/m^2)	21.60 ± 4.36	21.31 ± 4.23	NS[a]	21.52 ± 4.10	21.59 ± 4.13	21.61 ± 3.50	NS[c]
Waist circumference (cm)	71.19 ± 9.27	69.65 ± 7.28	NS[a]	70.54 ± 8.05	71.25 ± 8.92	72.67 ± 7.78	NS[c]
Passive smoking exposure, *n* (%)	163 (21.3)	22 (16.7)	NS[b]	63 (25.8)	105 (19.6)	17 (14.7)	NS[b]

Data presented as numbers and per cent within parenthesis, mean ± SD as appropriate.
[a]Statistical significance assessed using the *t*-test.
[b]Statistical significance assessed using the χ^2 test.
[c]Statistical significance assessed using the ANOVA test.
[d]Significant between 1, 2 and 2, 3 groups.

Table 2. Relation of menstrual pattern to calcium and vitamin D level.

	Serum Vitamin D			Corrected serum calcium			
Variable	Deficiency ≤15 ng/ml	Non-deficient >15 ng/ml	*p* value	Hypocalcaemia ≤2.17 mmol/l	Normal 2.17–2.47 mmol/l	Hypercalcaemia ≥2.47 mmol/l	*p* value
Age at menarche (year), mean ± SD	12.46 ± 1.34	12.57 ± 1.12	NS[a]	12.40 ± 1.10	12.52 ± 1.45	12.48 ± 1.02	NS[c]
Average days of bleeding, *n* (%)							
Short bleeding periods (4 d)	37 (4.8)	7 (5.3)	NS[b]	16 (6.6)	24 (4.4)	4 (3.4)	NS[b]
Normal periods (4–7 d)	617 (80.6)	110 (83.3)		191 (78.6)	448 (83.6)	88 (74.6)	
Long periods (>7 d)	111 (14.6)	15 (11.4)		36 (14.8)	64 (11.6)	26 (31.0) (22.0)	
Duration of the menstruation cycle, *n* (%)							
≤21 d	170 (22.2)	23 (17.6)	NS[b]	54 (22.2)	99 (18.5)	40 (33.9)	NS[b]
21–35 d	555 (72.6)	106 (80.2)		176 (72.4)	407 (75.9)	78 (66.1)	
≥35 d	40 (5.2)	3 (2.2)		13 (5.4)	30 (5.6)	0 (0)	
Menstrual flow, *n* (%)							
Little	196 (25.6)	25 (18.9)	NS[b]	84 (34.5)	124 (23.2)	13 (10.9)	**.005**[b]
Moderate	559 (73.0)	101 (76.5)		154 (63.2)	405 (75.5)	101 (85.9)	
Heavy	10 (1.4)	6 (4.4)		5 (2.3)	7 (1.3)	4 (3.2)	
PMS							
Yes	359 (46.9)	65 (49.2)	NS[b]	115 (47.3)	249 (46.4)	60 (45.5)	NS[b]
No	406 (53.1)	67 (50.8)		128 (52.7)	259 (53.6)	58 (54.5)	
Use of medication, *n* (%)							
Yes	293 (37.2)	42 (29.6)	NS[b]	107 (44.1)	182 (34.0)	46 (39.1)	NS[b]
No	472 (62.8)	90 (70.4)		136 (55.9)	354 (66.0)	72 (60.9)	
Classification of pain, *n* (%)							
Painless	46 (6.0)	11 (8.3)	NS[b]	20 (8.4)	32 (6.0)	5 (4.3)	NS[b]
Mild	351 (45.8)	62 (47.0)		90 (37.1)	272 (50.8)	51 (43.5)	
Moderate	189 (24.6)	25 (18.9)		68 (28.0)	110 (20.6)	36 (30.5)	
Severe	179 (23.6)	34 (25.8)		65 (26.5)	122 (22.6)	26 (21.7)	

Data presented as numbers and per cent within parenthesis and mean + SD as appropriate.
Significance of bold values is *p* value <.05.
[a]Statistical significance assessed using the *t*-test.
[b]Statistical significance assessed using the χ^2 test.
[c]Statistical significance assessed using the ANOVA test.

Table 3. Relation of physical symptoms of premenstrual syndrome (PMS) to calcium and vitamin D level.

	Serum Vitamin D			Corrected serum calcium			
Physical symptoms	Deficiency ≤15 ng/ml	Non-deficient >15 ng/ml	*p* value	Hypocalcaemia ≤2.17 mmol/l	Normal 2.17–2.47 mmol/l	Hypercalcaemia ≥2.47 mmol/l	*p* value
Abdominal pain							
Yes	561 (73.3)	96 (72.7)	NS	172 (70.6)	394 (73.7)	91 (76.8)	NS
No	204 (26.7)	36 (27.3)		71 (29.4)	142 (26.3)	27 (23.2)	
Foot pain							
Yes	167 (21.8)	31 (23.4)	NS	53 (21.7)	116 (21.6)	29 (24.6)	NS
No	598 (78.2)	102 (76.6)		190 (78.3)	420 (78.4)	89 (75.4)	
Backache							
Yes	475 (62.9)	80 (62.6)	NS	146 (60.1)	330 (61.6)	79 (66.7)	NS
No	290 (37.1)	52 (37.4)		97 (39.9)	206 (38.4)	39 (33.3)	
Nausea							
Yes	60 (7.9)	12 (9.6)	NS	27 (11.2)	42 (7.9)	3 (2.9)	NS
No	705 (92.1)	60 (90.4)		216 (88.8)	494 (92.1)	115 (97.1)	
Vomiting							
Yes	19 (2.5)	6 (4.5)	NS	12 (4.9)	10 (1.9)	3 (2.9)	NS
No	746 (97.5)	127 (95.5)		231 (95.1)	526 (98.1)	115 (97.1)	
Diarrhoea							
Yes	25 (3.2)	6 (4.5)	NS	12 (4.9)	17 (3.2)	2 (1.4)	NS
No	740 (96.8)	127 (97.5)		231 (95.1)	519 (96.8)	116 (98.6)	

Data presented as numbers and per cent within parenthesis.
Statistical significance assessed using the χ^2 test.

three calcium categories but the mean age was higher in normal calcium group compared to the other two groups.

There were no significant differences between the groups with regard to age at menarche, menstrual bleeding length, menstrual cycle length, and PMS. But, the menstrual flow of participants differed significantly from the calcium status groups ($p = .005$).

The incidence of physical symptom of PMS was similar in the three groups, and there were no significant differences observed between the groups.

The frequency of the most common psychological symptom did not differ significantly between the groups compared to other two groups ($p > .05$). But, the prevalence of irritability was significantly higher in the hypercalcaemia and

Table 4. Relation of psychological symptoms of premenstrual syndrome (PMS) to calcium and vitamin D level.

	Serum Vitamin D			Corrected serum calcium			
Symptoms	Deficiency ≤15 ng/ml	Non-deficient >15 ng/ml	*p* value	Hypocalcaemia ≤2.17 mmol/l	Normal 2.17–2.47 mmol/l	Hypercalcaemia ≥2.47 mmol/l	*p* value
Appetite changes							
Yes	3 (0.4)	0 (0)	NS	3 (1.4)	0 (0)	0 (0)	NS
No	762 (99.6)	132 (100)		240 (98.6)	536 (100)	118 (100)	
Irritability							
Yes	51 (6.7)	4 (2.3)	NS	16 (6.4)	23 (4.2)	16 (13.2)	**.018**
No	714 (93.3)	128 (97.7)		227 (93.6)	513 (95.8)	102 (86.8)	
Fatigue							
Yes	70 (9.2)	11 (10.0)	NS	19 (7.8)	45 (8.4)	17 (14.7)	NS
No	695 (90.8)	121 (90.0)		224 (92.2)	491 (91.6)	101 (85.3)	
Palpitation							
Yes	70 (9.2)	13 (10.0)	NS	21 (8.5)	50 (9.3)	12 (10.3)	NS
No	695 (90.8)	119 (90.0)		222 (91.5)	486 (90.7)	106 (90.8)	
Lack of energy							
Yes	85 (11.1)	15 (11.4)	NS	33 (13.5)	48 (9.0)	19 (16.2)	NS
No	680 (88.9)	117 (89.6)		210 (86.5)	488 (91.0)	99 (83.8)	
Sleep pattern changes							
Yes	4 (0.5)	0 (0)	NS	4 (1.5)	0 (0)	0 (0)	NS
No	761 (99.5)	132 (100)		239 (98.5)	536 (100)	118 (100)	
Depression and sadness							
Yes	68 (8.9)	14 (10.6)	NS	29 (11.9)	44 (8.3)	9 (7.4)	NS
No	697 (91.1)	118 (89.4)		214 (88.1)	492 (91.7)	109 (92.6)	
Decrease interest							
Yes	100 (13.1)	16 (12.2)	NS	33 (13.5)	60 (11.2)	23 (19.4)	NS
No	665 (86.9)	116 (87.8)		210 (86.5)	476 (88.8)	95 (80.6)	
Loss of concentration							
Yes	223 (29.1)	36 (27.2)	NS	76 (31.1)	156 (29.1)	27 (22.5)	NS
No	542 (70.9)	96 (72.8)		167 (68.9)	380 (70.9)	91 (77.5)	
Tendency to cry easily							
Yes	252 (32.9)	40 (30.3)	NS	80 (33.1)	167 (31.1)	45 (38.2)	NS
No	513 (67.1)	92 (69.7)		163 (66.9)	369 (68.9)	73 (61.8)	

Data presented as numbers and per cent within parenthesis.
Significance of bold values is p value $<.05$.
Statistical significance assessed using the χ^2 test.

hypocalcaemia groups compared to the normal calcium level group ($p = .018$).

Relationship between serum 25OHD level, menstrual bleeding pattern and PMS

The mean serum 25(OH)D concentration was 9.41 ng/ml (standard deviation: 8.9), with a median of 6.8 ng/ml (IQR: 4.0, 10.1 ng/ml). Most of the girls [85.3% ($n = 755$)] had a serum vitamin D concentration 25(OH)D level below 15 ng/ml and 14.7% ($n = 132$) had a serum vitamin D concentrations 25(OH)D level above 15 ng/ml.

No differences were found in the BMI, height, weight, smoking exposure or physical activity between the two vitamin D categories, but the mean age of the participants was slightly higher in the non-deficient group (Table 1). The vitamin D deficient and non-vitamin D deficient cases did not differ significantly with respect to menstrual disorders and PMS (Tables 2 and 3).

There were no statistically significant differences in the prevalence of physical, psychological and behavioural symptoms of PMS between the vitamin D deficient and vitamin D non-deficient groups (Tables 3 and 4). Moreover, serum 25(OH)D and albumin-corrected calcium levels could not predict the risk of PMS, whether it was a continuous variable or as a categorical variable (Table 5).

Table 5. Logistic regression analysis of serum vitamin D and calcium as a predictor of premenstrual syndrome (PMS), using different groups of vitamin D and calcium.

	OR	CI	*p* value
25(OH)D as continuous variable	0.996	0.981–1.011	.578
25(OH)D as categorical variable			
25(OH)D ≤ 15 ng/ml	ref	–	–
25(OH)D > 15 ng/ml	0.955	0.644–1.418	.821
Corrected calcium as continuous variable	0.736	0.312–1.734	.492
Corrected calcium as categorical variable			
Calcium ≤2.17 mmol/l	ref	–	–
2.17 mmol/l < Calcium <2.47 mmol/l	1.318	0.740–2.350	.349
Calcium ≥2.47 mmol/l	1.394	0.825–2.356	.215

Discussion

PMS was a common finding in our study subjects, and this has been reported to be a frequent menstrual problem in other populations (Bertone-Johnson et al. 2005; Obeidat et al. 2012; Konapur and Nagaraj 2014). Our cross-sectional study suggests that high corrected serum calcium may have a significant association on the incidence of irritability. The study of Kia et al. showed that the low serum levels of calcium though, within the reference range, was in the PMS participants compared to the healthy controls (Kia et al. 2015). Furthermore, a daily consumption of calcium carbonate reduced the severity of the PMS symptoms versus the placebo (48% vs. 30%) (Thys-Jacobs et al. 1998). Bendich and Bertone-Johnson also demonstrated a positive effect of calcium administrations on improving PMS symptoms (Bendich 2000;

Bertone-Johnson et al. 2005). We also found that in the hypercalcaemia group, the majority of the participants presented moderate blood flow. The amount of blood loss during menstruation affects the overall quality of life of women (Davies and Kadir 2017), so, this may be clinically relevant.

There was a high prevalence of vitamin D deficiency in our population sample of healthy girls. However, the prevalence of PMS symptoms did not differ significantly in relationship to vitamin D status. Another study in Iran showed that there was no significant difference in vitamin D serum status between PMS and control groups (Kia et al. 2015). Thys-Jacobs and a co-researcher reported that serum 25(OH)D levels were significantly lower in PMS cases through three phases of the menstrual cycle, while $1,25(OH)_2D$ levels were not significantly higher in PMS cases at all phases of the menstrual cycle (Thys-Jacobs and Alvir 1995). In a further study, 25(OH)D levels were non-significantly lower in women with PMDD compared to healthy controls (Thys-Jacobs et al. 2007). Furthermore, Obeidat et al. reported that PMS has no relationship to levels of parathyroid hormone, vitamin D or dairy products consumption in dysmenorrheic college students (Obeidat et al. 2012). Jukic et al found lower plasma levels of 25(OH)D were linked with irregular cycles, but not with short or long cycles (Jukic et al. 2015). This discrepancy with our result may be due to the different population samples; cycle regularity may be varying between younger and older women.

Our results are also consistent with results from a previous longitudinal study conducted between 1991 and 2005 that showed that women with PMS did not differ with respect to plasma levels of 25(OH)D, total calcium or parathyroid hormone, compared to their matched normal controls (Bertone-Johnson et al. 2014).

The strengths of our study include a comprehensive assessment of the aspect of menstrual bleeding pattern in a large population sample. Despite the large sample size, there were several limitations. The cross-sectional nature of our study does not allow the inference of causality. Recall bias may be another potential problem, due to the use of a self-administered questionnaire. All results were based on self-reported symptoms, and most of the adolescent in this study had 25(OH)D deficiency which reduced the power of the study to detect any association between the dichotomous 25(OH)D exposure ($\leq$15 ng/ml vs. $>$15 ng/ml) and menstrual problems.

Conclusion

Menstrual disorders and PMS are common in adolescent girls. The results from this study show no relationship between serum vitamin D levels and PMS. Whilst corrected serum calcium was associated with menstrual blood loss and irritability, and would support the benefits of an adequate intake of vitamin D; this needs to be assessed by an intervention study.

Acknowledgements

This article was part of the PhD thesis (941524) of Afsane Bahrami. We are grateful to all study participants, their parents and school personnel.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was supported by grants [941524] (Sadeghnia) from the Mashhad University of Medical Sciences.

References

Bahrami A, Mazloum SR, Maghsoudi S, Soleimani D, Khayyatzadeh SS, Arekhi S. 2018. High dose vitamin D supplementation is associated with a reduction in depression score among adolescent girls: a nine-week follow-up study. Journal of Dietary Supplements 15:173–182.

Bahrami A, Sadeghnia H, Avan A, Mirmousavi SJ, Moslem A, Eslami S. 2017. Neuropsychological function in relation to dysmenorrhea in adolescents. European Journal of Obstetrics, Gynecology, and Reproductive Biology 215:224–229.

Baird D, Hill MC, Schectman JM, Hollis BW. 2013. Vitamin D and risk of uterine fibroids. Epidemiology (Cambridge, Mass) 24:447.

Bendich A. 2000. The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms. Journal of the American College of Nutrition 19:3–12.

Bertone-Johnson ER, Chocano-Bedoya PO, Zagarins SE, Micka AE, Ronnenberg AG. 2010. Dietary vitamin D intake, 25-hydroxyvitamin D 3 levels and premenstrual syndrome in a college-aged population. The Journal of Steroid Biochemistry and Molecular Biology 121:434–437.

Bertone-Johnson ER, Hankinson SE, Bendich A, Johnson SR, Willett WC, Manson JE. 2005. Calcium and vitamin D intake and risk of incident premenstrual syndrome. Archives of Internal Medicine 165:1246–1252.

Bertone-Johnson ER, Hankinson SE, Forger NG, Powers SI, Willett WC, Johnson SR, Manson JE. 2014. Plasma 25-hydroxyvitamin D and risk of premenstrual syndrome in a prospective cohort study. BMC Women's Health 14:1.

Davies J, Kadir RA. 2017. Heavy menstrual bleeding: an update on management. Thrombosis Research 151:S70–S77.

Delshad M, Ghanbarian A, Ghaleh NR, Amirshekari G, Askari S, Azizi F. 2015. Reliability and validity of the modifiable activity questionnaire for an Iranian urban adolescent population. International Journal of Preventive Medicine 6:3.

Dicken CL, Israel DD, Davis JB, Sun Y, Shu J, Hardin J, Neal-Perry G. 2012. Peripubertal vitamin D(3) deficiency delays puberty and disrupts the estrous cycle in adult female mice. Biology of Reproduction 87:51.

Evans KN, Bulmer JN, Kilby MD, Hewison M. 2004. Vitamin D and placental-decidual function. Journal of the Society for Gynecologic Investigation 11:263–271.

Freeman EW. 2003. Premenstrual syndrome and premenstrual dysphoric disorder: definitions and diagnosis. Psychoneuroendocrinology 28:25–37.

Gøransson LG, Skadberg Ø, Bergrem H. 2005. Albumin-corrected or ionized calcium in renal failure? What to measure? Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association – European Renal Association 20:2126–2129.

Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. 2004. Prevalence of vitamin D deficiency among healthy adolescents. Archives of Pediatrics & Adolescent Medicine 158:531–537.

Halbreich U. 2003. The etiology, biology, and evolving pathology of premenstrual syndromes. Psychoneuroendocrinology 28:55–99.

Halbreich U, O'Brien PM, Eriksson E, Bäckström T, Yonkers KA, Freeman EW. 2006. Are there differential symptom profiles that improve in response to different pharmacological treatments of premenstrual syndrome/premenstrual dysphoric disorder? CNS Drugs 20:523–547.

Hickey M, Balen A. 2003. Menstrual disorders in adolescence: investigation and management. Human Reproduction Update 9:493–504.

Jukic AMZ, Steiner AZ, Baird DD. 2015. Lower plasma 25-hydroxyvitamin D is associated with irregular menstrual cycles in a cross-sectional study. Reproductive Biology and Endocrinology 13:20.

Kia AS, Amani R, Cheraghian B. 2015. The association between the risk of premenstrual syndrome and vitamin D, calcium, and magnesium status among university students: a case control study. Health Promotion Perspectives 5:225.

Konapur KS, Nagaraj C. 2014. Dysmenorrhoea and premenstrual syndrome: frequency and effect on daily activities of adolescent girls in rural areas of Bangalore. International Journal of Medical Science and Public Health 3:1225–1228.

Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. 2009. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics 124:e362–e370.

Lasco A, Catalano A, Benvenga S. 2012. Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: results of a randomized, double-blind, placebo-controlled study. Archives of Internal Medicine 172:366–367.

Lerchbaum E, Obermayer-Pietsch B. 2012. Mechanisms in endocrinology: vitamin D and fertility: a systematic review. European Journal of Endocrinology 166:765–778.

Luk J, Torrealday S, Perry GN, Pal L. 2012. Relevance of vitamin D in reproduction. Human Reproduction 27:3015–3027.

Malloy PJ, Peng L, Wang J, Feldman D. 2009. Interaction of the vitamin D receptor with a vitamin D response element in the Mullerian-inhibiting substance (MIS) promoter: regulation of MIS expression by calcitriol in prostate cancer cells. Endocrinology 150:1580–1587.

Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M, Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. 2008. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 122:398–417.

Mortola J, Girton L, Beck L, Yen S. 1990. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. Obstetrics and Gynecology 76:302–307.

Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, et al. 2002. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. The American Journal of Clinical Nutrition 76:187–192.

Obeidat BA, Alchalabi HA, Abdul-Razzak KK, Al-Farras MI. 2012. Premenstrual symptoms in dysmenorrheic college students: prevalence and relation to vitamin D and parathyroid hormone levels. International Journal of Environmental Research and Public Health 9:4210–4222.

Panda DK, Miao D, Tremblay ML, Sirois J, Farookhi R, Hendy GN, Goltzman D. 2001. Targeted ablation of the 25-hydroxyvitamin D 1α-hydroxylase enzyme: evidence for skeletal, reproductive, and immune dysfunction. Proceedings of the National Academy of Sciences of the United States of America 98:7498–7503.

Proctor M, Murphy PA. 2001. Herbal and dietary therapies for primary and secondary dysmenorrhoea. The Cochrane Database of Systematic Review 3:CD002124.

Sava L, Pillai S, More U, Sontakke A. 2005. Serum calcium measurement: total versus free (ionized) calcium. Indian Journal of Clinical Biochemistry 20:158–161.

Tabatabaeizadeh SA, Avan A, Bahrami A, Khodashenas E, Esmaeili H, Ferns GA. 2017. High dose supplementation of vitamin D affects measures of systemic inflammation: reductions in high sensitivity C reactive protein level and neutrophil to lymphocyte ratio (NLR) distribution. Journal of Cellular Biochemistry 118:4317–4322.

Thys-Jacobs S. 2000. Micronutrients and the premenstrual syndrome: the case for calcium. Journal of the American College of Nutrition 19:220–227.

Thys-Jacobs S, Alvir M. 1995. Calcium-regulating hormones across the menstrual cycle: evidence of a secondary hyperparathyroidism in women with PMS. The Journal of Clinical Endocrinology and Metabolism 80:2227–2232.

Thys-Jacobs S, McMahon D, Bilezikian JP. 2007. Cyclical changes in calcium metabolism across the menstrual cycle in women with premenstrual dysphoric disorder. The Journal of Clinical Endocrinology and Metabolism 92:2952–2959.

Thys-Jacobs S, Starkey P, Bernstein D, Tian J, Group PSS. 1998. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. American Journal of Obstetrics and Gynecology 179:444–452.