Biological Trace Element Research (2019) 192:145–152
https://doi.org/10.1007/s12011-019-01672-z

The Association Between Serum Magnesium and Premenstrual Syndrome: a Systematic Review and Meta-Analysis of Observational Studies

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Received: 27 December 2018 / Accepted: 7 February 2019 / Published online: 18 March 2019

Abstract

A number of studies have assessed the association between serum magnesium (Mg) and premenstrual syndrome (PMS) in different population, but the findings have been inconclusive. Herein, we systematically reviewed available observational studies to elucidate the overall relationship between Mg and PMS. PubMed, Cochrane's library, ScienceDirect, Scopus, Google Scholar, and ISI web of science databases were searched for all available literature until January 2019 for studies evaluating the association between Mg and PMS. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of observational studies. A total of 13 studies out of 196 met our inclusion criteria and were included in our systematic review and meta-analysis. There were no associations between serum magnesium and PMS (WMD − 0.04; 95% CI, − 0.14 to 0.06; $P = 0.46$) during follicular or serum/erythrocyte magnesium (WMD − 0.37; 95% CI, − 1.01 to 0.27; $P = 0.25$)/(WMD − 0.04; 95% CI, − 0.10 to 0.03; $P = 0.26$) and during luteal phase except for the sub-group of studies done outside of the US in which recent association became significant and means that serum Mg is lower in PMS subjects. According to what have been discussed, although our study did not show any significant association between serum/erythrocyte Mg and PMS except for serum Mg in luteal phase in the sub-group of studies done outside of the USA, heterogeneity between studies should be taken into accounts when interpreting these results. Additional well-designed clinical trials should be considered in future research to develop firm conclusions on the efficacy of magnesium on PMS.

Registration number: CRD42018114473.

Keywords Magnesium · Premenstrual syndrome · PMS · Systematic review · Meta-analysis

Introduction

Premenstrual syndrome (PMS) is defined as a cyclic disorder with predictable psychological and physical symptoms that occur in the late luteal phase of menstrual cycle. The main symptoms are dizziness, palpitations, headache, edema, mastalgia, abdominal pains, anxiety, depressive mood, agitation, and aggression [1]. Generally, symptoms are mild, but 5–8% of women experience severe PMS, which is called premenstrual dysphoric disorder (PMDD) [2].

There are different hypotheses contributed to PMS etiology, including endocrine factors such as hypoglycemia, hyperprolactinemia, and fluctuations in the levels of circulating estradiol and progesterone. The other etiology of PMS might be excessive amounts of aldosterone or antidiuretic hormone or lower nocturnal melatonin concentrations, neurotransmitter involvement, including serotonin and gama-aminobutyric acid. None of these hypotheses have been scientifically supported [1], and, so far, the main etiology of PMS as same as the

This manuscript has not been published elsewhere or submitted for publication elsewhere.

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PMDD remains unclear [3]. The symptoms of PMS may be serious enough to disturb women's regular living, quality of life, and social relationships and lead to amplified rates of suicides, accidents, joblessness, work and school absenteeism, and poor scholastic execution. Besides, reproductive health issues such as child abuse and domestic violence have also been documented in families with individuals experiencing PMS. This syndrome not only impacts the individual herself, but also has consequences for the family and even the society [4]; therefore, sufficient attention is needed to decrease its undesirable effects.

Based on current literature, many different pharmacological treatments, including hormone therapy have been recommended as possible options for women with PMS [5]. These therapies may be applicable to resolving PMS in many women, but they are also associated with significant unfavorable effects and can be expensive. Alternatives to hormone therapy, such as dietary supplementation, are being evaluated [6]. Non-pharmacologic management with some evidence for efficacy includes cognitive-behavioral relaxation therapy, aerobic exercise, as well as calcium, magnesium, vitamin B6 or L-tryptophan supplementation or intake of complex carbohydrate [7].

Magnesium (Mg) is a cofactor of more than 300 enzymes systems, which were contributed to diverse biochemical reaction regulations such as protein synthesis, muscle and nerve function, blood-glucose control, and blood pressure regulation [8]. Abnormal Mg metabolism has been reported in several neuropsychiatric disorders with prominent mood and physical symptoms, including migraine, epilepsy, and chronic pain [9–12]. Because PMS is associated with symptoms such as mood instability, fatigue, and fluid changes and share some similar characteristics with Mg deficiency symptoms, it has been hypothesized that there is a relationship between Mg and PMS [3].

Not all studies, however, have established either differences in Mg levels among women with PMS and control subjects or improvement in PMS symptoms in response to the administration of Mg [13–15]. Thus, the importance of Mg in the pathophysiology, diagnosis, and treatment of PMS remains unclear. Therefore, the aim of the current study was to carry out a systematic review and meta-analysis on the observational studies investigating the association between serum/erythrocyte Mg levels and PMS in general populations to reach a conclusion in this regard.

Methods and Materials

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and was registered on Prospero database (CRD42018114473) [16].

Data Source and Search Strategy

We searched databases, including PubMed, Scopus, Cochrane Library, ScienceDirect, and ISI web of sciences up to December 2018 to identify relevant studies. The reference lists of the included papers were also reviewed to discover additional eligible studies. The following search strategy was run in PubMed and tailored to each database when necessary: ((((Magnesium [MeSH Terms]) OR Mg [Title/Abstract]) AND premenstrual syndrome [MeSH Terms]) OR premenstrual tension[Title/Abstract]) OR PMS[Title/Abstract].

Inclusion Criteria

To be included in the study, publications investigating the association between serum Mg and PMS or its symptoms had to meet the following criteria: (1) original articles; (2) human studies with no restrictions on study parameters (study duration, design or sample size); (3) adequate data to calculate a relevant measure of association (mean, range or interquartile range); (4) articles published in English. Articles were excluded if they were of non-human studies, review articles, case reports, editorials, and poster abstracts.

Data Extraction

Pairs of independent reviewers (A.A and H.H) screened the titles and the abstracts of each study prior to full-text screening of nominee studies. Any divergences in terms of the decision on a given study were dealt with via discussion and if necessary, arbitration by a third reviewer. For all included studies, two reviewers independently extracted information, including first author's name, year of publication, country, sample size, participants' age, gender, study design, dietary and PMS assessment method, and statistical adjustment.

Study Quality

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of each study [17]. The scale consists of assessment of three domains: selection (5 points), comparability (2 points), and outcome (3 points) for a total score of 10 points. Studies scoring 7–10, 3–6, and 0–3 points were identified as high, moderate, and low quality, respectively [18].

Statistical Analysis

Meta-analysis was performed using weighted mean difference (WMD) with 95% confidence intervals (CIs) for assessing the association between serum Mg level and PMS. If heterogeneity is presented between studies, the random effects model was used, otherwise, the fixed effects model was used. The

sensitivity analyses were also performed to assess the influence of each individual study on the stability of the meta-analysis results. Each time, one study was excluded to show the study's impact on the combined effect estimate.

Assessment of Heterogeneity

Heterogeneity of the study results was estimated by the chi-squared (χ^2) test and quantified using the I^2 statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than to chance. I^2 was calculated using the formula: $I^2 = 100\% \times (Q - \mathrm{df})/Q$ (where Q is the chi-squared statistic, and df is the degrees of freedom), and an I^2 value of 75% or greater was deemed to indicate a high level of inconsistency. Significant heterogeneity was defined with a P value of < 0.05 [18].

Assessment of Publication Bias

Publication bias as was assessed by visual inspection of funnel plots and Egger's and Begg's tests was conducted to determine the degree of funnel plot asymmetry with $P < 0.05$ representing significant publication bias [18].

Results

Search Results

Our initial search through databases identified a total of 361 articles. Removing duplicates yielded 134 articles, which were reviewed based on the title and abstract by two independent reviewers. Seventy-nine papers retrieved and reviewed based on full text which 13 articles met inclusion criteria and were included in our systematic review and meta-analysis. The PRISMA flow diagram summarizes the results of the study selection process for this systematic review and meta-analysis (Fig. 1).

Overview of Included Studies

A total of 13 studies, including 11 case-control [3, 14, 19–28] and 1 cross-sectional [29] which involved 813 participants were included in our systematic review and meta-analysis. The included studies were conducted between 1981 and 2017. Among included studies, 7 were from USA [3, 20, 21, 23, 25, 27, 29], 2 Iran [19, 26], and the others were established from Italy [22], Australia [14], UK [28], and Turkey [24]. Five studies [3, 20, 22, 25, 28] measure Mg levels in both serum and erythrocyte, 7 in serum [14, 19, 21, 23, 24, 26, 29], and only 1 in erythrocyte [27]. Only 5 studies [3, 21, 23, 26, 29] assessed the dietary intake of participants, and the others did not mention anything [14, 19, 20, 22, 24, 25, 27, 28]. Among

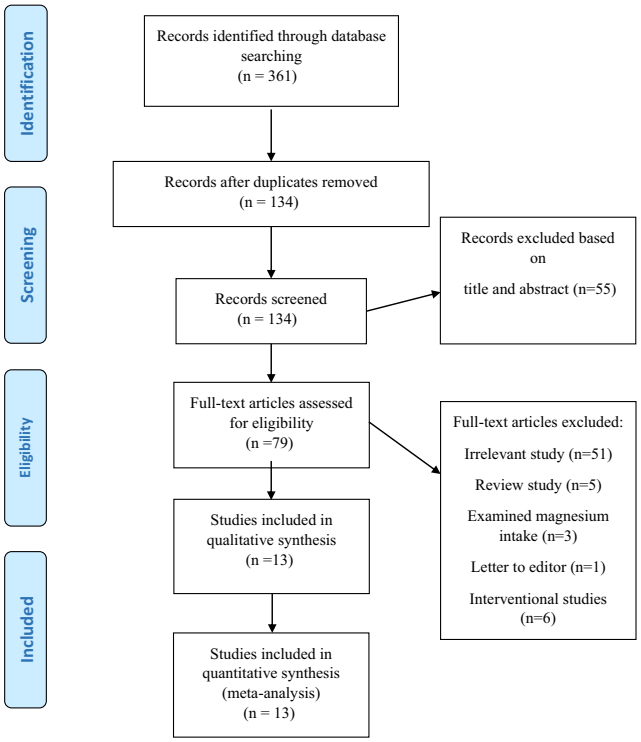

Fig. 1 The flow diagram of study selection

included studies, 12 studies [3, 14, 20–29] identified as moderate and 1 as low quality [19], respectively. Characteristics of included studies are illustrated in Table 1.

The Association Between Serum Mg and PMS During Follicular Phase

Five studies with 215 participants examined the association between serum Mg and PMS among subjects with and without PMS during follicular phase [14, 21, 22, 24, 25]. There was no significant association between serum Mg and PMS (WMD − 0.04; 95% CI, − 0.14 to 0.06; $P = 0.46$). There was evidence of heterogeneity between the effect sizes of included studies ($I^2 = 63.9\%$ $P = 0.02$). No evidence of publication bias was found (Begg's test; $P = 0.32$, Egger's test; $P = 0.36$) (Fig. 2).

The Association Between Serum Mg and PMS During Luteal Phase

Thirteen studies with 813 participants examined the association between serum Mg and PMS among subjects with and without PMS during luteal phase [3, 14, 19–29]. There was no significant association between serum Mg and PMS (WMD − 0.04; 95% CI, − 0.10 to 0.03; $P = 0.26$). There was evidence of heterogeneity between the effect sizes of included studies ($I^2 = 80.8\%$ $P < 0.001$) so we have done sub-group analysis based on the studies' location (USA vs outside of the USA).

Table 1 Characteristics of observational studies

Author, Year	Location	Sample size	Age range	Study design	DAM	PMSAM	Results		Quality score
							Serum	RBC	
Thys-Jacobs et al., 2007	USA	115	18–45	Cross-sectional	Food record	Self-assessment symptom-rating questionnaires (PMSD)	NS	–	6/10
Saeedian Kia et al., 2015	Iran	62	20–25	Case control	24-h recall questionnaire	Utah PMS calendarII	Serum Mg were reduced in PMS subjects	–	6/9
Shamberger et al., 2003	USA	96	19–52	Case control	NM	NM	–	NS	5/9
Chuong et al., 1994	USA	20	24–39	Case control	24-h recall questionnaire	Menstrual distress questionnaire	NS	–	5/9
Abraham et al., 1981	USA	35	23–44	Case control	NM	NM	NS	RBC Mg were reduced in PMS subjects	5/9
Facchinetti et al., 1990	Italy	29	21–39	Case control	NM	Menstrual distress questionnaire	NS	NS	5/9
Gallant et al., 1987	USA	19	18–45	Case control	Food record	PDSR	NS	–	5/9
Khine et al., 2006	USA	31	20–43	Case control	24-h recall questionnaire	VAS	NS	NS	5/9
Rosenstein et al., 1994	USA	45	22–48	Case control	NM	VAS	NS	NS	6/9
Sherwood et al., 1986	UK	155	36 ± 8.7	Case control	NM	MOOS questionnaire	NS	RBC Mg were reduced in PMS subjects	6/9
Abbasi et al., 2017	Iran	85	18–28	Case control	NM	NM	Serum Mg were reduced in PMS subjects	–	3/9
Mira et al., 1988	Australia	61	20–45	Case control	NM	PDSR	NS	–	5/9
Posaci et al., 1994	Turkey	60	20–45	Case control	NM	Menstrual distress questionnaire	Serum Mg were reduced in PMS subjects	–	5/9

DAM dietary assessment method, *MSAM* premenstrual syndrome assessment method, *PMS* premenstrual syndrome, *COPE* calendar of premenstrual experiences, *PSST* premenstrual syndrome screening tool, *SRQ* self-reported questionnaire, *GHLQ* general health and lifestyle questionnaire, *FFQ* food frequency questionnaire, *IU* international unit, *BMI* body mass index

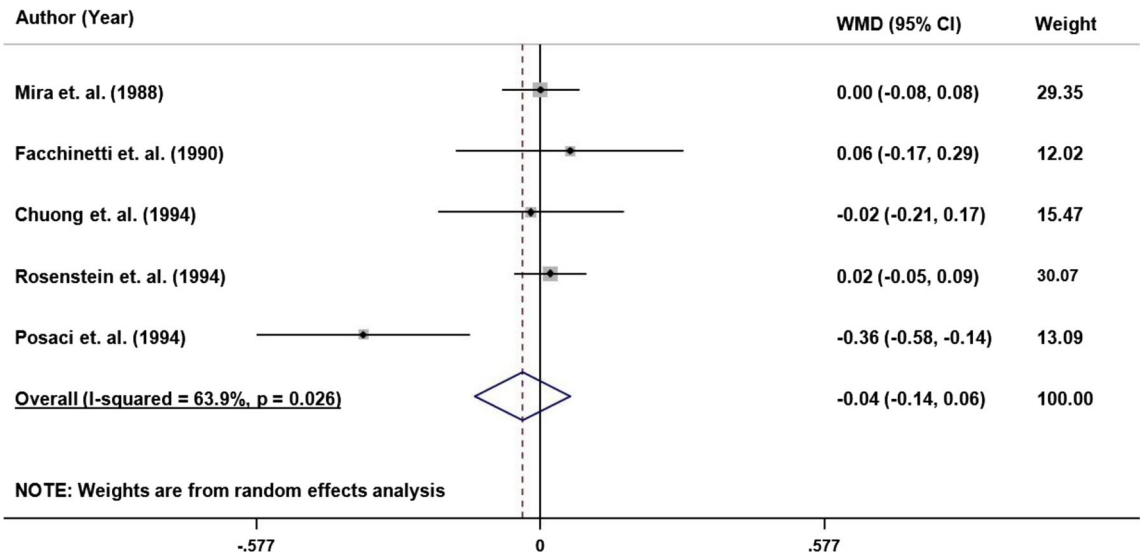

Fig. 2 Forest plot of the association between serum magnesium and PMS during follicular phase

The heterogeneity decreased significantly in a sub-group of studies done in the USA ($I^2 = 22.4\%$ $P = 0.25$), but there was no significant result (WMD − 0.04; 95% CI, − 0.01 to 0.09; $P = 0.12$) in this subgroup too. On the other hand, in the sub-group of studies done outside of the USA, the recent association became significant which means that serum Mg is lower in PMS subjects, but there is still evidence of heterogeneity in this sub-group. No evidence of publication bias was found (Begg's test; $P = 0.62$, Egger's test; $P = 0.85$) (Fig. 3).

The Association Between Erythrocyte Magnesium and PMS During Luteal Phase

Five studies with 295 participants examined the association between erythrocyte Mg and PMS among subjects with and without PMS during luteal phase [3, 14, 19–29]. There was no significant association between erythrocyte Mg and PMS (WMD − 0.37; 95% CI, − 1.01 to 0.27; $P = 0.25$). There was evidence of heterogeneity between the effect sizes of included studies ($I^2 = 91.5\%$ $P < 0.001$). No evidence of publication bias was found (Begg's test; $P = 0.32$, Egger's test; $P = 0.36$) (Fig. 4).

Discussion

To the best of our knowledge, no systematic review and meta-analysis has been published to evaluate the association between serum/erythrocyte Mg and PMS in general populations. Therefore, we gathered all the observational studies which examined recent relationship. In our analysis, we did not find any significant association between serum/erythrocyte Mg

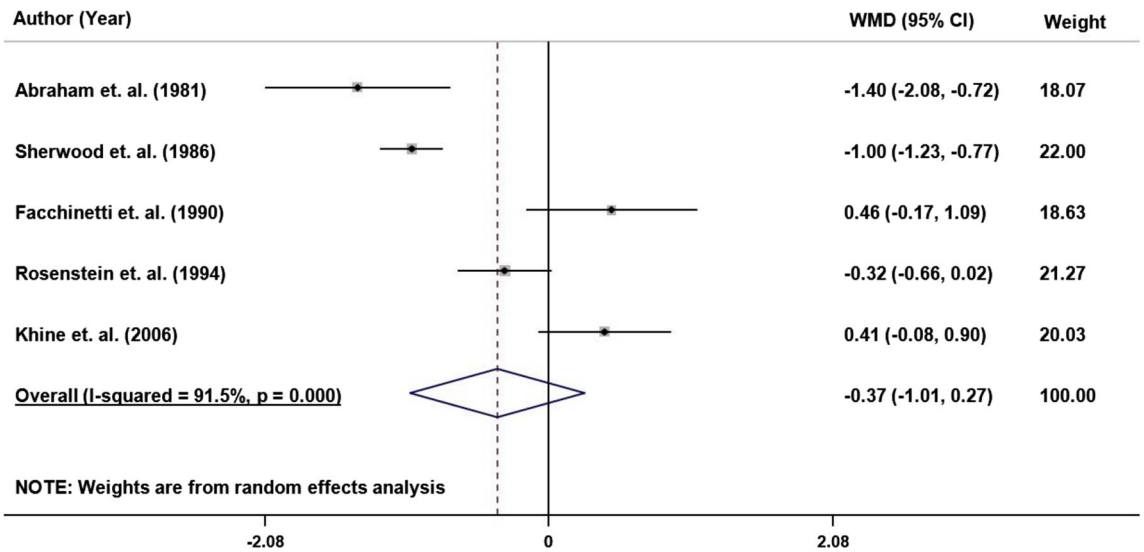

Fig. 3 Forest plot of the association between erythrocyte magnesium and PMS during luteal phase

and PMS either in luteal or follicular phase except for serum Mg in luteal phase in the sub-group of studies done outside of the USA. Some points should be taken into accounts when interpreting these findings.

In the analysis of erythrocyte Mg during luteal phase, the difference between PMS and healthy subjects is not significant, which is in line with previous reports [3, 22, 25]. It should be mentioned that all the included studies in this category are rated as moderate quality based on NOS. One of the probable explanations for this discrepancy is that red cell Mg is not a good indicator of Mg nutritional status [22]. On the other hand, none of these studies assessed or adjusted nutritional intake of participants which could affect the overall result.

Analysis of serum Mg during luteal and follicular phase did not show any significant difference in PMS and healthy controls except for sub-group of studies done outside of the USA. These findings are consistent with previous reports [3, 21–23, 25, 27]. Additionally, the included studies in this category are rated as moderate quality. A probable explanation for this finding could be described by "vulnerability hypothesis" mentioned that women with PMS have the vulnerability to luteal phase mood state destabilization, and Mg deficiency may act as one of a number of potential factors contributing to that vulnerability. This hypothesis also explained why some PMS patients have normal Mg concentration, and some other Mg-deficient subjects did not show any symptoms of PMS [25, 30, 31]. Moreover, Shamberger et al. suggested that the interaction of the two elements may be more consequential to PMS than either element alone. It means that, for example, Ca/Mg ratio is more important in PMS subjects than dietary amounts of either elements [27]. Furthermore, it should be noticed that vitamin and mineral levels in blood do not parallel those in the central nervous system. It means that bioavailability of Mg in the central nervous system which is linked to the activities of several neurotransmitters could change during the luteal phase of some patients with PMS, but these changes in central nervous system may not be reflected in the blood level [21, 32].

In addition to Mg roles in brain dopamine depletion and increasing insulin sensitivity, its deficiency could promote an increased pituitary and adrenal response to environmental stimuli with increased aldosterone secretion [33–35]. Mg is known to increase the threshold for stressful stimuli and decrease the secretion of aldosterone, which is responsible for water retention in PMS [36]. Mg deficiency has led to aldosterone elevation, which could increase the urinary excretion of Mg and resulting in its further deficiency [37]. Mg deficiency in PMS patients may be due to decreased intake/absorption or increased renal excretion [20]. PMS subjects often complain of nervous tension which these stress, stimulated secretion of mineralocorticoids and glucocorticoids. Glucocorticoids decrease intestinal absorption, and mineralocorticoids increase

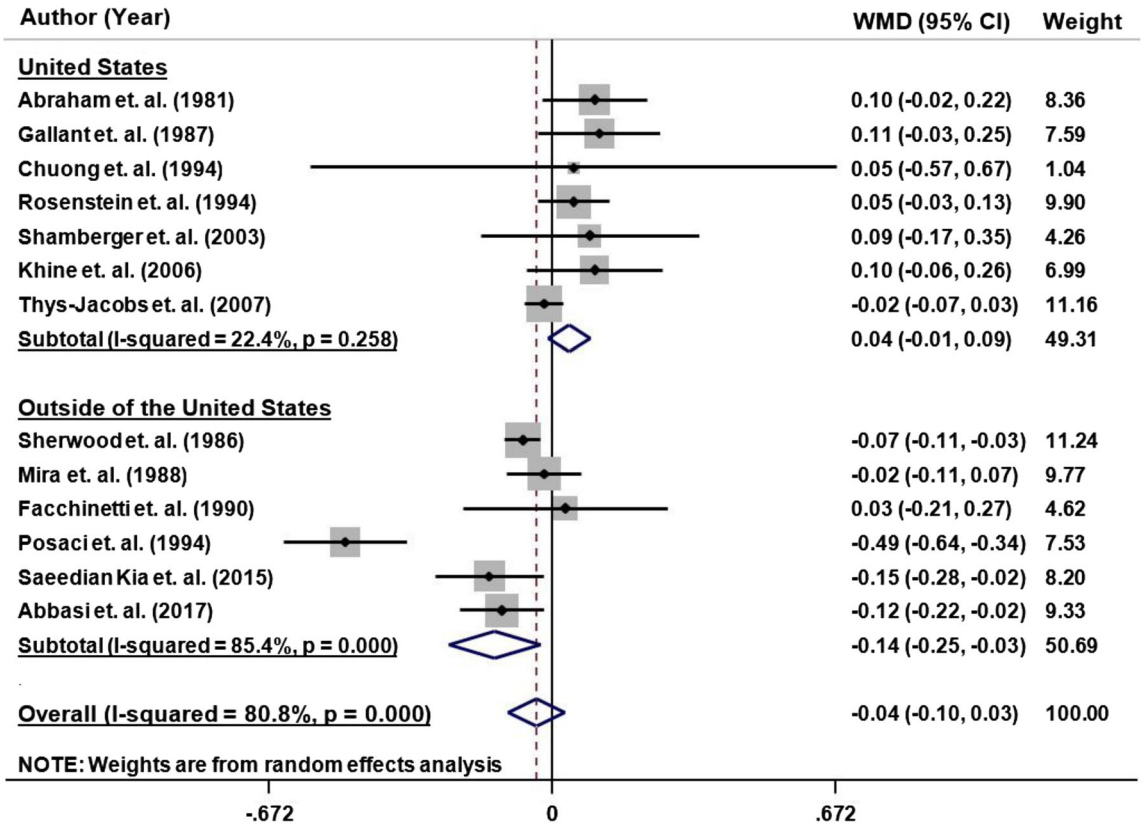

Fig. 4 Forest plot of the association between serum magnesium and PMS during luteal phase

renal excretion of Mg. Combined with poor eating habits, Mg depletion can occur rapidly among patients with PMS. Although PMS could have led to Mg depletion, many of the PMS symptoms could be explained by Mg deficiency [20, 26, 38]. Furthermore, it has been reported that Mg deficiency could deplete brain dopamine, possibly leading to mood disturbance, and hypertrophy of adrenal cortex leading to fluid retention [39, 40]. Mg is known as the endogenous antagonist of calcium, and the presence of selective Mg channels inside the plasma membranes is linked with membrane stabilizing properties of this cation. Reproductive hormones, progesterone and estrogen, seems to play a regulatory role on Mg balance [22]. Progesterone displays an Mg-retentive action, but estrogen has the opposite effects. The levels of recent hormones were similar in patients with PMS and healthy controls, which suggested that the ovarian function was not the primary cause for reduced Mg in PMS patients [22].

The present study has some limitations that warrant consideration. First, significant heterogeneity was present in our analysis that would limit the generalization of our findings. Heterogeneity between studies may be explained by the number of participants, participant's different serum Mg levels, different methods for assessment of PMS and Mg, and different population and adjusted models. Moreover, designs of included studies were case-control, which were prone to selection bias. Third, small sample size of included studies. Furthermore, most of the included studies did not assess dietary intake of participants, and the others which done this measurement did not adjust the effects of dietary intake of Mg. Also genetic characteristics of participants may impact on Mg concentration and overall results which this point did not mention in included studies.

There is no previous systematic review, and meta-analysis assessed the association between serum/erythrocyte Mg and PMS in observational studies which this point is our study strength.

Conclusion

According to what have been discussed, although our study did not show any significant association between serum/erythrocyte Mg and PMS except for serum Mg in luteal phase in the sub-group of studies done outside of the USA, heterogeneity between studies should be taken into accounts when interpreting these results. Additional well-designed clinical trials should be considered in future research to develop firm conclusions on the efficacy of magnesium on PMS.

Author Contribution H. Hajianfar and A. Arab contributed in conceptualizing the manuscript and editing the draft.

A. Arab, M. Moslehi, and M. Shadnoush contributed in writing and revising the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interests.

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