

Magnesium in the gynecological practice: a literature review

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Abstract. A growing amount of evidence suggests that magnesium deficiency may play an important role in several clinical conditions concerning women health such as premenstrual syndrome, dysmenorrhea, and postmenopausal symptoms. A number of studies highlighted a positive correlation between magnesium administration and relief or prevention of these symptoms, thus suggesting that magnesium supplementation may represent a viable treatment for these conditions. Despite this amount of evidence describing the efficacy of magnesium, few and un-systematized data are available about the pharmacological mechanism of this ion for these conditions. Herein, we review and systematize the available evidence about the use of oral magnesium supplementation in several gynecological conditions and discuss the pharmacological mechanisms that characterize these interventions. The picture that emerges indicates that magnesium supplementation is effective in the prevention of dysmenorrhea, premenstrual syndrome, and menstrual migraine and in the prevention of climacteric symptoms.

Key words: magnesium, dysmenorrhea, menopause, premenstrual symptoms

Magnesium is the fourth most abundant cation in the human body and is well known to be implied in several important functions such as enzyme activity, DNA and protein synthesis, and neuromuscular excitability [1, 2]. Approximately 99% of the total body magnesium is stored intracellularly, predominantly in bones, muscles, and soft tissues [1, 3].

Serum magnesium concentration is strictly regulated by the balance between intestinal absorption, renal excretion, and bone buffer [2]. The absorption of magnesium occurs predominantly in the small intestine and depends on two different pathways: a passive paracellular absorption, which facilitates bulk magnesium absorption, and an active transcellular pathway responsible for mediating the fine-tuning of magnesium absorption [1, 4-6].

In the kidney, 80% of total serum magnesium is filtered in the glomeruli, with >95% being reabsorbed in the nephron [1]. Renal reabsorption of magnesium represents an important mechanism to maintain magnesium homeostasis: it may decline to nearly zero in the presence of hypermagnesaemia and increase to over 99% in the presence of magnesium depletion [1].

The third pivotal player in the regulation of magnesium serum level is the bone: approximately 50-60% of total magnesium resides as surface substituents of the hydroxyapatite mineral component of the bone [2, 7]. This provides a large exchangeable pool to buffer acute changes in serum magnesium concentration and may therefore mask magnesium deficiency. Taken together, these mechanisms strictly maintain magnesium homeostasis [1].

Despite the presence of this system, a number of physiological and pathological conditions may cause deficiency of this ion. Such a condition, defined as hypomagnesaemia, may be asymptomatic or associated with a large variety of clinical features [1].

A growing amount of evidence suggests that magnesium deficiency may also play an important role in several clinical conditions such as premenstrual syndrome, dysmenorrhea, and postmenopausal-related symptoms. A number of studies have also suggested that magnesium supplementation may represent a viable treatment for these conditions, with several reports describing positive correlation between magnesium administration and relief or prevention of these symptoms [4, 8, 9]. Despite several reports describing the clinical efficacy of supplementation with this ion, fewer and un-systematized data are available for what concern the pharmacological mechanisms behind the use of magnesium for these conditions.

Such a topic is of importance as magnesium is available in a number of different formulations for both oral and parenteral use, thus providing a viable and inexpensive treatment.

The aim of this analysis is to summarize current evidence about the role of oral magnesium supplementation in several clinical conditions of gynecological interest such as premenstrual syndrome, dysmenorrhea, and postmenopausal disorders. When available, data describing the pharmacological mechanism behind the efficacy of this intervention were reviewed and systematized.

Dysmenorrhea

Dysmenorrhea is defined as painful uterine cramps that precede or accompany menses [6, 10]. This condition is likely to be related to the presence of myometrium hyper contractility and arteriolar vasoconstriction [11, 12]. The pathological mechanism behind this condition has been largely analyzed: it is well known that after ovulation there is a buildup of omega-6 fatty acids within the cell membranes. Before menstruation the progesterone levels decrease and omega-6 fatty acids, particularly arachidonic acid, are released [11, 12]. Such release initiates the cascade of prostaglandins and leukotrienes in the

uterus [13], which in turn induce an inflammatory response and lead to the onset of cramps and other systemic symptoms such as nausea, vomiting, bloating, and headaches [11, 12].

Suggested treatments for dysmenorrhea include the use of combined oral contraceptive pills, nonsteroidal anti-inflammatory drugs (NSAIDs), as well as other nonpharmacological interventions such as herbal preparations, transcutaneous nerve stimulation, acupuncture, and heat therapy [6, 10].

The potential role for magnesium in the treatment of dysmenorrhea has been investigated in three placebo-controlled studies included in a Cochrane review publication [14]. One small parallel trial showed that magnesium was significantly more effective than placebo after six months of daily treatment [15]. This datum was further confirmed in another small trial enrolling 21 patients treated for five months [14, 16], but not in a third analysis carried out in a four-month trial [17]. A fourth open trial found that magnesium therapy greatly reduced symptoms compared with the pretreatment control cycles [18].

The mechanism of action of magnesium in this setting has not been fully elucidated, but an interesting hypothesis could be formulated considering the calcium antagonist activity of this ion on smooth muscle. Such a mechanism has already been proposed to explain the inhibition of uterine contractility observed both in vivo and in vitro after magnesium sulfate administration for the prevention of preterm birth.

Taken together these data suggest that magnesium is effective and may represent an effective option for the treatment and the prevention of dysmenorrhea.

Menstrual migraine

Menstrual migraine represents a very common finding for gynecologist. Studies estimated that about 50% of women have suffered of migraines related to menstrual cycle [19, 20]. Menstrual-related migraine begins at menarche and can be associated with other somatic complaints related to the fall of sex hormone levels. Attacks of menstrual migraine may occur with or without aura and are usually more debilitating, more prone to recurrence, and less responsive to acute treatment than nonmenstrual migraine attacks [21].

The mechanism behind the onset of this condition has been widely studied and appears to be related to the withdrawal of estrogens, which are known to modulate both neuronal activity and receptor density [21].

The treatment of menstrual migraine could be classified as acute or preventive. Treatment in acute settings is well studied and includes the use of NSAIDs, triptans, ergot derivatives alone or in combination with antiemetic [21].

While a significant amount of evidence exists for the acute treatment, only few evidence are available for the prevention of migraine attacks. Possible preventive treatments include perimenstrual estrogen, short-term NSAID, and perimenstrual triptans [21].

The efficacy of magnesium supplementation for the prevention of premenstrual migraine has been evaluated in a number of studies. Peikert *et al.* [22] carried out a placebo-controlled trial to evaluate the efficacy of daily oral magnesium for 12 weeks and found a 41.6% reduction in the frequency of migraine attacks in the magnesium arm compared with a 15.8% reduction in the placebo group. A similar result was reported by Bigal *et al.* [23], but was not confirmed in a third analysis [24].

The mechanism by which magnesium supplementation may reduce the frequency of migraine attacks was not fully elucidated, nor it was the mechanism by which the lack of magnesium may trigger this condition. However, a number of hypotheses have been proposed: It is well known that the lack of magnesium may promote platelets hyperaggregation and cortical depression spreading, impair serotonin receptor function, and influence neurotransmitters synthesis and release [25]. All of these mechanisms have been related to the pathogenesis of migraine [25].

Another important aspect of migraine onset is represented by psychological stress. It is widely recognized that daily emotional and physical stressors, such as financial worries, job, and relationship concerns can trigger migraine attacks in some people. Such events are more likely to induce an attack when the migraine threshold is lowered as it is for many female migraineurs in the perimenstrual period [26].

In this view, the correlation between lack of magnesium and stress has been highlighted in a number of observational studies in both acute and chronic setting [27]. Such a datum was further

strengthened by the observation that magnesium supplementation may improve emotional stress response in preclinical models [28, 29].

Premenstrual symptoms

Premenstrual syndrome (PMS) is a condition characterized by the onset of physical, affective, and behavioral symptoms during the luteal phase that significantly impairs the daily lives [30, 31]. This condition was estimated to affect up to 80-90% of females in reproductive age [32].

One of the proposed approaches for the prevention of PMS is the supplementation with magnesium, alone or in combination with vitamin B6. This therapeutic approach is supported by the finding that magnesium level of women with PMS is lower than that in healthy women [33]

Several studies were carried out to evaluate the efficacy of magnesium supplementation for the prevention of PMS: Facchinetti *et al.* [8] carried out a trial enrolling 32 women with PMS treated with magnesium or placebo, from the 15th day of the menstrual cycle to the onset of menstrual flow. Premenstrual syndrome symptoms, measured with an appropriate questionnaire, decreased in magnesium arm but not in placebo arm. Consistently, intracellular magnesium level increased significantly following supplementation. The efficacy of magnesium in PMS was further confirmed by Walker *et al.* [9] and Quaranta *et al.* [34].

Of interest, the results of these studies suggest that at least two months are required for the presentation of the therapeutic effects of magnesium [35].

Magnesium supplementation was also evaluated in combination with vitamin B6 and was found to be more effective than magnesium alone and placebo in decreasing PMS symptoms [35, 36].

The mechanism by which magnesium is effective to reduce PMS symptoms has not been fully elucidated, but several hypotheses have been proposed. As the larger improvements are usually observed in the symptoms related to emotional and behavioral components, such as depression, irritability, tiredness, and anxiety, it has been proposed that magnesium acts primarily by normalizing the actions of different hormones (mainly progesterone) on the central nervous system [34].

Menopause

Menopausal women suffer from a variety of symptoms including hot flashes, night sweats, mood swings, insomnia, and long-term complications such as osteoporosis. These symptoms arise primarily as a response to the decline in circulating endogenous estrogens, but a growing amount of evidence suggests that magnesium deficiency may play a pivotal role in these conditions.

Climacteric symptoms

Mood disorders represent a very common finding in peri- and postmenopausal women, affecting up to 90 % of these subjects. Magnesium deficiency has been related to the onset and the severity of depression and anxiety in animal models: magnesium-deficient diet was proven to enhance depression and anxiety-related behavior in mice [28, 29] and magnesium supplementation was reported to induce an antidepressant effect in mice [24, 37, 38].

Such findings were confirmed in a recent observational study reported by Stanisławska *et al.* [39], who found significantly lower magnesium concentrations in women with depressive symptoms compared with healthy controls.

Another common symptom of menopause is the occurrence of hot flashes. Two recent analyses [40, 41] focused on the efficacy of magnesium oxide supplements to reduce the incidence of hot flashes in women with a history of breast cancer. The results provided discordant results, with the larger analysis being carried out by the North Central Cancer Treatment Group reporting no difference between the treatment and the placebo arm. As these analyses were not carried out in women with age-related menopause, further studies aimed at defining the role of magnesium in the treatment of this symptom in subjects suffering from natural menopause would be of importance.

Osteoporosis

Dietary magnesium deficiency has also been implicated as a risk factor for osteoporosis, which represent a well-known long-term risk for postmenopausal women. Such correlation was consistently highlighted in both preclinical, clinical, and epidemiological studies, thus providing

important insight on the importance of magnesium supplementation in older women [7].

Preclinical studies showed that young growing animals exposed to magnesium deficiency present significant abnormality in bone tissue including reduction in trabecular bone mass, increased fragility, and decreased number and organization of chondrocytes [42, 43].

Epidemiological studies highlighted a significant link between dietary Mg inadequacy and osteoporosis: A positive correlation was reported between Mg intake, appendicular BMD [5], and bone mass of the forearm [5]. Additionally, Mg intake was found to be negatively correlated with urinary excretion of pyridinoline and deoxypyridinoline, thus suggesting that a low-Mg diet is associated with an increased bone resorption [5].

In another study involving perimenopausal and postmenopausal women, patients with severe osteoporosis were found to have significantly lower serum levels of ionized Mg [44]. Gur *et al.*, who found lower mg levels in osteoporotic subjects compared with nonosteoporotic postmenopausal women [45], further confirmed this datum.

While several population-based studies have proved the beneficial effects of calcium supplementation in postmenopausal osteoporosis [46], fewer evidence exist on the possible role of magnesium supplementation. Aydin *et al.* [47] recently reported that short-term oral magnesium supplementation raises serum levels of osteocalcin and significantly decreases markers of bone resorption.

Although still fragmentary, the current amount of evidence suggests that magnesium is an important factor for bone health and that the optimization of the intake of this ion might represent an effective and low-cost preventive measure against osteoporosis.

Discussion and conclusion

A number of conditions of gynecological interest have been related to magnesium deficiency. Current evidence suggests that for some of these conditions, such as PMS, menstrual migraine, and dysmenorrhea, a clear relationship between magnesium deficiency and symptoms occurrence exists and that magnesium supplementation may reduce or abolish clinical symptoms. For other conditions, such as those related to climacteric

syndrome, data are less robust and further studies are required. Of interest, magnesium supplementation has been also proposed for conditions, such as osteoporosis, for which large population-based studies have already provided important evidence on the role of mineral supplementation.

In the routine gynecological practice, these findings have an important impact and should be considered together with the well-recognized role of magnesium in pregnancy, when the Mg homeostasis generally maintained through intake via food and drinking water is impaired by an increased metabolism and a state of inflammation in the placenta and blood vessels [48] and there is an increased demand by the fetus. This impairment is more evident in women with preeclampsia. In these women erythrocyte membrane, brain, muscle and maternal and umbilical cord blood Mg levels were lower than in normal pregnancies [49-52]. Along this line several studies have found that Mg supplementation decreases the risk of pregnancy complications and high increase in blood pressure and preeclampsia [52].

Despite the grooving amount of evidence suggesting the importance of magnesium, a number of recent studies showed that the vast majority of European and United States population has a magnesium intake that falls below the daily-recommended amount. Such datum is of importance as magnesium deficiency may impact a number of conditions related to women health. In this setting, a proper supplementation with magnesium may represent a viable and inexpensive intervention, which has been proved to be effective in a number of conditions, including those related to women health.

Magnesium is administrated as organic or inorganic compounds. Such conjugation is well known to affect both magnesium bioavailability and absorption. However, scarce information exists to detail which is the best magnesium salt to be used in human supplementation.

In a recent analysis, Coudray *et al.* [53] reported that organic forms of magnesium were more absorbable than inorganic ones as assessed by intestinal absorption and urinary excretion. Among the organic forms, no major differences were reported in terms of absorption or excretion [53]. Of interest, it was suggested that the magnesium organic salt containing pidolic acid may improve intracellular concentration faster than other salts, thus providing an advantage in a number of selected clinical setting requiring fast

effects such as dysmenorrhea or migraine. In view of the importance of magnesium supplementation, further analyses are required to fully elucidate the differences between various magnesium salts.

Further attempts are also required to evaluate the relationship between magnesium deficiency and specific clinical condition: in some cases, such as for the clear link between hypomagnesaemia and cardiac arrhythmias, this relationship is well described and is nowadays well recognized [1]. Yet, the understanding of the role of magnesium for the human health is rapidly changing and a number of new conditions have been linked to hypomagnesaemia. An interesting example of such a link is represented by psychological stress: Several preclinical studies have recently highlighted the relationship between low magnesium levels and stress-related behavior in mice and other animal models. Similar observations were also reported in humans, with significant relationship described with depression, anxiety, and other symptoms.

Of interest, an animal model of stress suggested that different magnesium salt may have different effects on stress behavior. In particular, magnesium pidolate showed the greatest efficacy on repeated experimental setting, thus suggesting a higher acute anti-muricidal, and perhaps anti-stress effect.

Psychological stress has been described to have an important role as a trigger for migraine, including the ones occurring in the premenstrual period. In this view, the relationship between stress, magnesium deficiency, and migraine attack should be further explored and clarified.

Taken altogether, the evidence reviewed in this paper suggests an important role for magnesium for the prevention and the treatment of a number of conditions relevant for women health. Further studies are required to better define the role of magnesium supplementation in conditions such as emotional stress and to fully elucidate the mechanism of action of magnesium in several of these conditions.

Disclosure

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