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Magnesium supplementation in Obstetrics and Gynaecology: a brief review

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ABSTRACT

Magnesium (Mg), is the second most important intracellular cation. It has been recognized as a cofactor for more than 325 enzymatic reactions involved in a) protein, DNA and RNA synthesis, b) fat, carbohydrates and protein metabolism, and c) cellular energy production and storage. It is essential for the regulation of muscular contraction, blood pressure, insulin metabolism, cardiac excitability, vasomotor tone, nerve transmission and neuromuscular conduction.
On these grounds, the possible therapeutic properties of Mg have been investigated in almost every medical field including Obstetrics and Gynecology, namely exploring oral supplementation.
The aim of this study is to briefly review existing evidences on the clinical effects of Mg treatment in perinatology as well as in non-pregnant women.
During pregnancy, there is a 15% decrease of Mg circulating levels together with a concomitant 25% increase of urinary excretion. Mg supplementation on blood pressure had few impact while it is useful for the alleviation of uterine hyperactivity. Parenteral administration is a standard for the prophylaxis of Eclampsia as well as for neural protection of early preterm baby.
A number of studies highlighted a positive correlation between oral magnesium and relief/ prevention of premenstrual syndrome, dysmenorrhea, and postmenopausal symptoms, thus suggesting that magnesium supplementation may represent a valid treatment for these conditions.

SOMMARIO

Il magnesio è il secondo più importante catione intracellulare implicato in numerose funzioni fisiologiche. Partecipa come cofattore alle reazioni enzimatiche di più di 325 enzimi per a) la sintesi delle proteine, DNA, RNA, b) il metabolismo di carboidrati lipidi e proteine, c) la produzione e l'immagazzinamento di energia intracellulare.
Partecipa inoltre al trasporto di calcio e potassio attraverso le membrane cellulari, meccanismo fondamentale per la trasmissione dell'impulso nervoso e la conduzione neuromuscolare.
Regola il tono della muscolatura, l'eccitabilità del miocardio, la pressione arteriosa ed ha un ruolo anche nel controllo del metabolismo glucidico. Le proprietà ed i possibili effetti terapeutici del magnesio sono stati ampiamente studiati.
In ginecologia ed ostetricia sono numerose le ricerche volte a valutare l'efficacia di un supplemento orale di magnesio. L'obiettivo di questo studio è di effettuare una breve revisione della letteratura a disposizione sugli effetti clinici del Magnesio sia in ambito materno fetale che ginecologico. Durante la gravidanza si verifica una riduzione del 15% dei livelli di magnesio circolante con un concomitante aumento del 25% della sua escrezione urinaria.
Numerosi studi hanno dimostrato che una supplementazione di Magnesio in gravidanza è poco utile per il controllo della pressione arteriosa, ma molto efficace nel ridurre l'ipercontrattilità uterina. Il magnesio solfato i.v. inoltre trova applicazione nella prevenzione dell'eclampsia, e per la neuroprotezione fetale dei feti pretermine.
Ampie evidenze sostengono la somministrazione orale di magnesio per la riduzione o la prevenzione di sintomi correlati alla sindrome premestruale, nella profilassi della dismenorrea e nelle donne in menopausa.

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INTRODUCTION

Magnesium (Mg), the second most important intracellular cation, plays several fundamental physiological roles, namely being involved in neuro-muscular junction as well as in vascular contractility. Such biological activities are mediated either through cellular channels exchanges as well acting as co-factor of more than 325 enzymatic reactions involved in a) protein, DNA and RNA synthesis, b) fat, carbohydrates and protein metabolism, and c) cellular energy production and storage (1).
On these grounds, the possible therapeutic properties of Mg have been investigated in almost every medical field. Indeed, two international, peer-reviewed Journals published research reports since 1991.
A growing number of researches is available in Obstetrics and Gynaecology, namely exploring oral supplementation. While i.v. Mg should administered with caution because efficacy dosage could engender toxic concentrations, administration per os have been reportedly safe, without risk of over-dosage, unless kidney function is severely affected.
The reason why supplement magnesium are several. In some circumstances there may be a chronic or a transient (oral contraception, pregnancy) deficiency while in the most part of the cases the cation could exert beneficial effects, supporting vulnerable conditions.
The aim of this study is to briefly review existing evidences on the clinical effects of Mg treatment in perinatology as well as in non-pregnant women.

MAGNESIUM ABSORPTION AND METABOLISM

Magnesium availability in the body is regulated by intestine, bone and kidneys, passive absorption in the intestine assuring the main entrance. Kidney represents the main regulator of excretion. The homeostasis of Mg is also under endocrine control, namely by 1,25 -dihydroxy Vitamin D, parathyroid hormone and estrogens.
In the presence of a physiological organ functioning, experimental data indicate that the main factor affecting Mg absorption is represented by the quality of the salt to which the cation is coupled. In general terms organic salts such as pidolate are better absorbed that inorganic salts like oxide an citrates (2).
Interestingly, a recent pharmaceutical technology using sucrose esters has been reported to significantly improve Mg absorption. *Ex vivo* and experiment demonstrated that sucrosomial magnesium better passes intestinal barrier and urine excretion was several times increased after treatment respect with Mg oxide, citrate and bysglycinate (2).
However, in order to achieve an adequate supplementation, it has to be remembered that almost the total body content of Mg is distributed in the intracellular compartment. The target of any supplementation would therefore increase Mg content into the cell (3).

MAGNESIUM SUPPLEMENTATION IN GYNAECOLOGY

Dysmenorrhea

Dysmenorrhea is one of the most common menstrual disorder in women of reproductive age, defined as the presence, at the beginning of menstrual flow, of severe pelvic pain, often associated with autonomic symptoms, such as nausea, vomiting, diarrhea and fatigue. This condition occurs few hours before the menstrual flow, reaches its peak after a maximum of 48 hours, and can compromise the usual daily activities.
Numerous studies demonstrate the central role of prostaglandins (PGs) and leukotrienes in the pathogenesis of dysmenorrhea, leading to local and systemic inflammatory process (4, 5). The pathogenesis

of pelvic pain can be explained by the local inflammation that determines myometrium hyper-contractility and arteriolar vasoconstriction (4, 5).
Validated treatments for dysmenorrhea include combined oral contraceptive pill, nonsteroidal anti-inflammatory drugs (NSAIDs), non-pharmacological interventions such as herbal preparations, transcutaneous nerve stimulation, acupuncture, and heat therapy (6).
The beneficial role of magnesium in the treatment of dysmenorrhea has been evaluated in three placebo-controlled studies, included in a Cochrane review publication (7).
Fifty patients suffering from primary dysmenorrhea were included in a double-blind study, conducted by Seifert *et al*. This study demonstrates the efficacy of magnesium in terms of reduction of symptoms in 21 women out of 25 (8). In another controlled study, the therapeutic effect of magnesium has been investigated in 32 women, 11 treated with magnesium and 10 with placebo. The effect of magnesium in terms of back pain and lower abdominal pain was significantly evident after 3 days of administration (9, 10).
There is also a fourth open trial which found that magnesium treatment greatly reduced symptoms compared with the pretreatment control cycles (10).
The mechanism of action of magnesium in dysmenorrhea can be explained by its antagonist role towards calcium on smooth muscle, causing relaxation of the myometrium (8).
These data suggest that magnesium is important and may represent a real option for the treatment and the prevention of this pathological condition.

Premenstrual syndrome

Premenstrual syndrome (PMS) includes a wide variety of physical, psychological, and cognitive symptoms that occur recurrently and cyclically during the luteal phase of the menstrual cycle and disappear soon after the onset of menstruation (11, 12).
Although the etiology of these disorders remains uncertain, research suggests that altered regulation of neuro-hormones and neurotransmitters is involved (13), all of them being modulated by cyclical estradiol and progesterone changes.
Several studies were carried out to evaluate the efficacy of magnesium supplementation for the prevention of PMS (14) since many years.
Facchinetti *et al*. carried out a trial enrolling 32 women with PMS which were treated with magnesium pidolate (360 mg/day) or placebo, from the 15th day of the menstrual cycle to the onset of menstrual flow. PMS symptoms, measured with an appropriate questionnaire, decreased in the group treated with magnesium but not in the placebo group (15).
In a pilot study conducted by Quaranta *et al.* there are new evidence supporting the utility of magnesium supplementation in the treatment of PMS and suggest that magnesium may improve symptoms for these women. This is because magnesium level in women with PMS is lower than in healthy women (16). This evidence is also supported in a study conducted by Donald L *et al*.
The purpose of this study was to evaluate blood magnesium measures across the menstrual cycle in women affected by PMS and control women.
Longitudinal determinations of levels of magnesium in plasma, red blood cell and mononuclear blood cell were made in 26 women with confirmed PMS and in a control group of women.
They found decreased levels of magnesium in women affected by PMS. The mechanism by which magnesium is effective to reduce PMS symptoms has not been fully elucidated, but there are several hypotheses. It has been proposed that magnesium normalizes the actions of different hormones, mainly progesterone, on the central nervous system (13, 14, 16).

Menopausal women

Menopause is the time of life when menstrual cycles cease, and is caused by reduced secretion of the ovarian hormones. Women experience a variety of symptoms and conditions related to changes in sex hormone levels (17, 18). Hormonal changes, in particular hypo-estrogenemia, that start during the menopausal transition affect many biological systems.
The signs and symptoms of postmenopausal women include involve several systems and lot of evidences suggest that magnesium deficiency plays an important role also at menopause (19, 20).

Osteoporosis
Osteoporosis is the leading cause of fractures in the population older than 50 years and it affects primarily postmenopausal women (21). Magnesium deficiency contributes to osteoporosis directly by acting on crystal formation and on bone cells and indirectly by impacting on the secretion and the activity of parathyroid hormone (22) . Aydin *et al.* recently reported that short-term oral magnesium supplementation raises serum levels of osteocalcin and significantly decreases markers of bone resorption (23).

Cardiovascular disorders
Magnesium deficiency is associated with cardiovascular diseases. It is involved in blood pressure regulation with the important role of modulating vascular tonus. Indeed, Mg deficiency increases angiotensin II, aldosterone synthesis and the production of thromboxane and prostaglandins (24).
A recently published meta-analysis of 22 trials with 1173 normotensive and hypertensive adults concluded that Mg supplementation for a period of 3-24 weeks significantly decreased systolic and diastolic blood pressure (25).
A systematic review and meta-analysis of prospective studies that comprised 313,041 individuals and 11,995 cardiovascular diseases, 7534 ischemic heart diseases, and 2686 fatal ischemic heart disease events found that higher serum levels of magnesium were significantly associated with a lower risk of the above reported disorders (5).

Central nervous system disorders
Magnesium plays also an important modulatory role in brain biochemistry, influencing several neurotransmission pathways associated with the development of mood disorders such as depression. Several mechanisms are responsible for these effects.
In a recent pilot study by Chouinard *et al*. chronic administration of magnesium aspartate hydrochloride (40 mEq/day) was effective in mood stabilization of 50% of manic-depressive subjects (26). It seems also that Mg supplementation is well-tolerated and enhances the efficacy of conventional antidepressant treatments (27).

Climacteric symptoms
Ma supplements seems to reduce the incidence of hot flashes in women with an history of breast cancer. This is of paramount importance since those women are at increased risk of cancer idf subumitted to hormone replacement treatments. In the study of Haeseong Parket et al. breast cancer patients with at least 14 hot flashes a week receive magnesium oxide 400 mg for 4 weeks and at the end of treatment oral magnesium appears to have helped more than half of the patients.

MAGNESIUM SUPPLEMENTATION IN OBSTETRICS

The utilization of Mg in pregnant women is based on its major property, *i.e*. being the endogenous calcium antagonist. This occur in the smooth muscle uterine and perivascular muscle cells where it counteract the endogenous Calcium release. Similary, Mg is a Ca antagonist in the neurons where it stabilizes the electrical activity. For this reason Mg Sulphate was first infused in pregnant women in 1916 for the managing of eclamptic bursts (28).
During pregnancy, there is a 15% decrease of Mg circulating levels together with a concomitant 25% increase of urinary excretion with an increased clearance of 41%.These values return to baseline after delivery and are not solely explained by fetal tissue accretion and/or maternal plasma dilution/expansion, but requires specific changes in renal function (29). Anyway, this define pregnancy a Mg-deficient condition.

Preterm contractions

Uterine contractility is under the control of several substances mainly including Oxytocin, PGs and alpha-1 agonists. Upon a receptor-mediated and/or a membrane surface stimulus (calcium-dependent and voltage-dependent channels, Nitric Oxide, *etc*.) intracellular mechanisms allow the release of Ca ion which combine with Calmodulin and this complex activate the phosphorylation of myosin light chain through a specific kinase. Several substances modulate those activities including Estradiol, Progesterone. The elegant in vivo experiment of Valenzuela demonstrated that also Mg could modulate uterine activity, namely inhibiting the frequency of uterine contractions (30).
Combining these properties and the observation of reduced Mg levels in pregnant women, different Authors tried to use Mg as a supplement to normal diet. In a controlled study published in the first volume of this journal, we reported that Mg supplementation (pidolate salt 300 mg/twice a day) increased the intracellular content of Mg, either in red blood cells and monocytes, after 4 weeks of treatment (15). Moreover, in a placebo-controlled, double-blind design about 600 women were randomized to receive 15 mMol/day Mg aspartate vs aspartate alone, within 16th week of pregnancy. The number of hospital admission, namely for cervical incontinence and preterm labour was significantly reduced in the Mg arm respect with placebo. Moreover, the percentage of low birthweight babies was significantly reduced from 8.2% in placebo to 2.8% in Mg group. No side effects were reported (31).
Since then, a lot of studies investigated the effects of Mg supplementation for preterm uterine con-

tractions. Diverse Mg salts were found equally effective than ritodrine and terbutaline in prolonging gestation. It has to be highlighted that the above mentioned selective beta agonists were banned from the European Medicine Agency due to their side effects and the poor evidences on their efficacy (32).

Pregnancy-induced hypertension

The Calcium antagonistic properties of Mg are effective in the perivascular muscle cells allowing arterial relaxation, also in the umbilical cord (33).
As a proof of concept, the urinary excretion of Mg was found to be negatively correlated with the Mean Arterial Pressure value (34). More convincing was the experiment performed by Tranquilli et al. They replicated the Gannt' experiment when progressively increasing dose of Angiotensin II there was a simultaneous increase in diastolic Blood Pressure. The concomitant infusion of Mg was able to counteract Angiotensin II effect and higher doses of the compound were requested to obtain the same increase of diastolic values (35).
From a clinical point of view, the ability of supplemental Mg to reduce the onset of gestational hypertension was controversial due to different salts and daily doses (36, 37).

Eclampsia/neural protection

Today, the efficacy of Mg infusion (in the form of Sulphate) for the prophylaxis of Eclampsia as well as for neural protection of early preterm baby is well established.
Magnesium sulfate (MgSO4) is the agent most commonly used for treatment of eclampsia and prophylaxis of seizures in patients with severe pre-eclampsia (PE). PE is a condition that complicates around 3-5% of pregnancies and it's defined as hypertension and proteinuria occurring after 20 weeks of gestation. It is usually classified as either mild or severe according to symproms (38).The most dangerous complication of severe PE is eclampsia, which is defined by general tonic-clonic convulsions before and/or after birth. Eclamptic seizure will occur in 2% of patients with severe PE who are not receiving magnesium sulfate, and in less than 0.6% in those receiving magnesium (39).The use of MgSO4 as seizure prophylaxis for the form of severe pre-eclampsia is supported by some important studies (40, 41).The mechanism by which parenteral MgSO4 prevents seizures is only partially understood. An hypothesis is that magnesium may inhibit NMDA receptors and block the neuronal damage associated with ischaemia (42, 43). Another possible mechanism is that MgSO4 may lead to cerebral vasodilatation, with reduction of cerebral ischaemia (44).
Magnesium has a beneficial effect also for fetal neuroprotection when very preterm delivery is imminent (45, 46). Among women delivering very low-birthweight infants, Nelson and Grether demonstrated an 86% risk reduction in cerebral palsy in children prenatally exposed to MgSO4 compared with unexposed controls (45). Schendel et al also showed that infants born to women who received the compound during pregnancy either for PE or tocolysis were almost 90% less likely to be born with cerebral palsy compared with those born to unexposed women. For those reasons antenatal MgSO4 is now recommended by the World Health Organization and many pediatric and obstetrical scientific societies.

CONCLUSIONS

In this brief review we summarized the clinical use of Mg adminstration in diverse Gynaecological and Obstetrical conditions.
While the use of parenteral MgSO4 is under strict hospital manipulation because of safety caution, the oral supplementation of Mg (coupled with different salts) is typically prescribed in the office, mainly due to efficacy and safety.
Mg supplementation has a room in the prophylaxis of both Dysmenorrhea and PMS where there is abundant literature confirming its efficacy. Easy of use and safety are added values of such intervention.
In pregnant women, oral Mg has demonstrated to be useful for the alleviation of uterine hyperactivity not linked to preterm labour.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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