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Magnesium in Women's Health and Gynecology

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Abstract

Magnesium is well known in the world of obstetrics for many important uses. It has been utilized in treating pre-eclampsia, eclampsia, and preventing preterm labor, though it has been found recently that prolonged magnesium administration in pregnant women may result in adverse outcomes to fetal bone metabolism, resulting in a new FDA warning [1]. Outside of obstetrics, magnesium is recommended for treating the arrhythmias torsades de pointes and rapid atrial fibrillation, treating severe acute asthma, improving migraine symptoms, and for treating dyspepsia and constipation [2]. Many women in our modern society are magnesium deficient due to low dietary intake, and low dietary magnesium intake resulting in hypomagnesaemia has recently been shown to have many deleterious effects. Magnesium's uses are wide-reaching, touching many areas of women's health and gynecology from pre-menstrual syndrome to menopause, PCOS to endometriosis, and beyond.

Keywords

Magnesium, Calcium, Hypomagnesemia, Women's Health

1. Introduction

Magnesium is the fourth most abundant essential mineral and the second most abundant intracellular divalent cation. It is involved as a cofactor for over 300 metabolic reactions in the body. Approximately 99% of total body magnesium is intracellular, with 85% stored in bone; only 1% is found within the extracellular space. Of magnesium present in serum, approximately 70% exists in the ionized (free) form, which is crucial to multiple physiologic processes [3]. Of these physiological processes, magnesium is involved in crucial processes such as

protein synthesis, adenylate cyclate synthesis, oxidative phosphorylation, cellular energy production and storage, preservation of cellular electrolyte composition, cell growth and reproduction, DNA and RNA synthesis, and stabilization of mitochondrial membranes [4]. In addition to its important role in cell biology and genetics, magnesium is also involved in bone metabolism, regulation of parathyroid hormone (PTH) secretion, nerve transmission, cardiac excitability, neuromuscular transduction, muscular contraction, vasomotor tone, and blood pressure regulation. Therefore, magnesium has demonstrated a wide range of possible effects on the human body that can thus affect women's health [5]-[7].

While magnesium is a crucial part of human biology, magnesium deficiency is widespread across different populations, as dietary magnesium intake has decreased dramatically, especially in the western world [2]. Some foods that are rich in magnesium are dark leafy green vegetables, beans, nuts, seeds, fish, whole grains, and dairy; these foods are often not heavily present in many western diets. A study of dietary intake of magnesium in US adults showed that women have a lower dietary intake of magnesium than men. Many women are deficient in magnesium due to both the highly processed magnesium-poor western diet and water softeners and purifiers that strip magnesium out of the drinking water supply. Furthermore, magnesium intake decreases with age. Of note, Caucasians have a significantly higher mean dietary intake of magnesium compared to African Americans [8]. In addition to dietary factors, many commonly prescribed medications can also lead to hypomagnesemia, such as diuretics (both loop and thiazide) and antimicrobials such as aminoglycosides, in addition to proton pump inhibitors that may decrease nutrient absorption; all of these medications are frequently in use among patients. Additionally, many chronic and acute illnesses can trigger magnesium wasting.

Magnesium deficiency may exacerbate chronic inflammatory stress and contribute to conditions such as atherosclerosis, diabetes, and osteoporosis [9]. In rats, inflammation has been found to occur during experimental magnesium deficiency; this low magnesium state also induces hypertriglyceridemia, atherogenesis, platelet aggregability, increased thrombotic events, and increased oxidative stress. It is hypothesized that magnesium deficiency may affect intracellular calcium homeostasis, linking inflammation and metabolic syndrome [10]. There is an inverse relationship between serum magnesium level and high-sensitivity C-reactive protein, an inflammatory marker. Decreased magnesium levels are associated with increased metabolic syndrome risk, as obesity itself is a low-grade inflammation process [11]. Regarding the role of hypomagnesemia in inflammation, adults with hypomagnesemia are found to have elevated CRP levels, while individuals with both hypomagnesemia and metabolic syndrome are also found to have elevated CRP levels [12]. The effects of magnesium on obesity are crucial to women's health, since women are more likely to be obese than men. Higher intake of magnesium is associated with lower BMI in middle aged US men and women, further supporting the link between low magnesium and obesity [13].

Magnesium's role in metabolic syndrome extends to diabetes mellitus. Higher magnesium intake may reduce the risk of developing type 2 diabetes mellitus [14]. Patients with non-insulin dependent diabetes and hypertension have been found to have poor intracellular magnesium concentrations. Magnesium can affect the role of insulin in a few ways. Insulin may modulate the shift of magnesium from extracellular to intracellular spaces; additionally, intracellular magnesium modulates insulin action by offsetting calcium-related excitation contraction coupling and decreasing smooth cell responsiveness to depolarizing stimuli [15]. Obese individuals with metabolic syndrome also commonly have low magnesium in serum and mononuclear cells, especially in non-white patients with insulin resistance. It is hypothesized that this hypomagnesemia may contribute to post-receptor insulin resistance on cells [16]. Magnesium may have a therapeutic role for diabetics in the future; experimental trials of 2.5 g magnesium chloride daily has also been found to improve the ability of beta cells to compensate for variations in insulin sensitivity in non-diabetic women with significant hypomagnesemia [17].

In addition to its role in obesity and diabetes, magnesium intake is associated with reduced mortality from cardiovascular disease in Japanese populations, especially women [18]. The biochemical basis behind the effects of magnesium deficiency on cardiovascular health are complex, involving oxidation of lipoproteins and effects on biochemical pathways leading to cardiovascular damage. Magnesium deficiency has been shown to result in down regulation of sphingomyelin synthase, along with a decreased synthesis of phosphatidylcholine, and an upregulation of cereamide synthase and biosynthesis of ceramides in cardiovascular tissue [19]. It is suggested that sphingolipids act as regulators of extracellular Mg^{2+} In a low magnesium state, ceramide synthase is upregulated in ventricular, atrial, aortic smooth muscles, in addition to the release of inflammatory cytokines [20]. Phosphatidylcholine is involved in decreasing the lymphatic absorption of cholesterol and is an important component of HDL, thus furthering the importance of magnesium for maintaining cardiovascular health. Addition-

ally, low magnesium levels can lead to increased apoptosis of cerebral vascular and peripheral vascular smooth muscle cells, in addition to an upregulation of certain proto-oncogenes that are also involved in atherogenesis and hypertension, including activation of the cell cycle regulator NF-κB and an upregulation of protein kinase C molecultes [21]-[24].

2. Premenstrual Syndrome

Magnesium has been hypothesized to possibly play a role in premenstrual syndrome (PMS). The erythrocyte concentration of magnesium in patients with PMS is significantly lower than that of patients without PMS [25]. It is hypothesized that this is because sex steroid hormones have modulate serum ionized magnesium and calcium levels throughout the menstrual cycle. In the follicular phase of the menstrual cycle, there is elevated serum Mg^{2+} and a decreased Ca^{2+}/Mg^{2+} ratio. However, at time of ovulation, there is a decrease in serum Mg^{2+}. During the luteal phase, there is decrease in Mg^{2+} and total Mg, as well as Ca^{2+}, proposed to be linked to peaked progesterone concentration. Peak in estrogen concentration is associated with elevated Ca^{2+}/Mg^{2+} ratio [26]. Changes in these serum cations can affect the various roles of Mg^{2+}, including vasculature, synaptic transmission, and excitation-contraction coupling. PMS occurs in the luteal phase when there is decreased Mg^{2+} and increased Ca^{2+}/Mg^{2+} ratio; it is proposed that women who are already magnesium deficient may be affected by this cyclical decreased in magnesium.

It has been suggested that many minerals may impact PMS. Limited evidence has suggested that magnesium supplementation, along with vitamin E and carbohydrate supplementation, may be useful for reducing PMS symptoms, while calcium supplementation was found to be of significant benefit [27]. A study showed that supplementation with both magnesium alone and magnesium plus vitamin B6 significantly decreased severity of PMS in an Iranian population, with the most significant benefit from magnesium plus B6 supplementation [28]. Another open-label preliminary study found that modified-release magnesium 250 mg tablet was effective in improving PMS symptoms in affected women [29]. Additionally, magnesium was shown to have some efficacy in treating menstrual migraines that occur with PMS [30]. However, a case-control study that assessed mineral intake using questionnaires found that while nonheme iron, potassium, and zinc affected PMS risk, magnesium was unrelated to PMS [31]. Additionally, a systematic review of randomized control trials to determine efficacy of 62 herbs, vitamins and minerals for reducing PMS symptoms found that only calcium had evidence to support use in treating PMS [32]. Further research is needed to explore the definitive role of magnesium in treating PMS.

3. Menopause

Magnesium is also hypothesized to have a role in menopause, due to the hormonal changes with magnesium demonstrated above. It has been found that there is an inverse relationship between estrogen concentration and serum Mg^{2+} and total Mg. Serum Ca^{2+} is also found to be significantly elevated in postmenopausal women. However, the ratio of Ca^{2+}/Mg^{2+} is not significantly elevated in postmenopausal women, and this ratio is a better indicator of cardiovascular problems that either cation alone [33]. Emerging research has also suggested that there is a link between menopausal hot flashes and cardiovascular disease risk, though the mechanisms underlying this association are unclear due to the incompletely understood physiology of hot flashes.

Magnesium has been explored to treat symptoms of menopause, including hot flashes and osteoporosis. Hot flashes have been found to be associated with a higher HOMA index, a measure of insulin resistance, and higher glucose levels to a more modest extent [34]. A pilot phase II trial of magnesium supplements to reduce menopause hot flashes in breast cancer patients found that patients who received magnesium oxide had 41.1% reduced hot flash frequency/week [35].

In dietary supplementation, postmenopausal women on hormone replacement therapy are often supplemented with calcium for osteoporosis treatment, yet are not routinely supplemented with magnesium. While calcium has benefits for bone health in postmenopausal women, low dietary intake of magnesium can be a risk factor for osteoporosis [36]. Magnesium homeostasis is important for bone health in addition to calcium, and low magnesium can affect bones in many ways, including mobilizing magnesium from the bone, slowing matrix calcification, and decreasing bone development, and decreasing bone strength [37] [38]. Additionally, low serum magnesium can decrease the secretion of parathyroid hormone and increase inflammation [29].

While hormonal replacement therapy is a controversial issue in menopausal treatment due to increased cardiovascular risk, it has been suggested that magnesium supplementation can decrease these coagulation risks. De-

creased dietary magnesium intake decreases serum magnesium levels, thereby increasing the Ca^{2+}/Mg^{2+} ratio and thus increasing blood clotting risk [39]. A decreased Ca^{2+}/Mg^{2+} ratio would decrease clotting risks. Menopausal women not being treated with hormonal replacement therapy have been found to have lower plasma levels of magnesium than menopausal women treated with hormonal replacement therapy [40]. Estrogen in hormonal replacement shifts magnesium from the circulation to soft and hard tissues. While calcium is often supplemented to treat osteoporosis, this supplementation plus decreased serum Mg^{2+} can lead to a higher Ca^{2+}/Mg^{2+} ratio and lead to intravascular coagulation risks. Magnesium also has antispasmodic effects on the smooth muscle of arteries, thus enhancing the neuroprotective effects of estrogen that may decrease with menopause [41].

4. Oral Contraceptives

Oral contraceptives affect serum levels of magnesium. While there are inherent changes with hormone levels discussed above, women on oral contraceptives may have changes in nutritional needs. Women on oral contraceptives are depleted of magnesium, in addition to selenium, zinc, and folic acid, and vitamins B2, B6, B12, C, and E, and may benefit from dietary supplementation [42]. The effect on magnesium is of note specifically because of the inherent risk of thromboembolic events while patients are on oral contraceptives and the effect magnesium has on thromboembolic events. In rat studies, rats that received oral contraceptive pills showed reduced glucose tolerance, reduced plasma HDL, increased plasma LDL, and increased atherogenic indices, while rats that received magnesium in addition to oral contraceptive pills showed less impaired glucose tolerance and less dyslipidemia [43]. Patients on contraceptives have been found to have decreased mean magnesium, zinc, selenium, and phosphorous compared to control groups. This reduction is proportional to the duration of time the patient has been using contraceptives. However, patients on contraceptives have also been found to have increased iron, calcium, and cadmium levels compared to control groups. This is important because it may increase a patient's Ca^{2+}/Mg^{2+} ratio, which increases cardiovascular risk in patients [44]. Further studies are needed to explore if magnesium supplementation in humans can decrease the clotting risk associated with OCPs.

5. PCOS

Polycystic ovarian syndrome (PCOS) is relevant to magnesium because of its associations with insulin resistance, obesity, and metabolic syndrome; as discussed above, low serum magnesium is associated with insulin resistance. It is unclear if there is a relation between magnesium and PCOS, as different studies have had varying conclusions. It has been shown that patients with PCOS have lower serum Mg^{2+} and higher serum Ca^{2+}/Mg^{2+} ratio, attributes that are associated with insulin resistance, cardiovascular problems, diabetes, and hypertension [45]. One study showed that PCOS patients specifically with insulin resistance exhibited lower serum levels of magnesium [46]. However, other studies have shown that serum magnesium concentrations are indistinguishable between women with and without PCOS, and that while PCOS patients were 19 times greater to have magnesium deficiency, no correlation was found between this decreased magnesium concentration and insulin resistance. After adjusting for calcium concentration, the relationship between magnesium and PCOS was insignificant [47] [48]. This suggests that calcium concentration is related to PCOS, however, which would affect the Ca^{2+}/Mg^{2+} ratio and thus cardiovascular risk factors. A study in which PCOS patients were treated with magnesium oxide showed no change in free fatty acids, which if elevated can result in the development of insulin resistance. However, this study used a dosage of 400 mg of magnesium oxide twice daily, while other studies have shown increased effects with higher doses of 2.5 g of magnesium chloride daily, suggesting that a higher dosage would be needed to reveal an effect [49]. A study in IVF patients undergoing ovarian hyperstimulation showed that an increase in serum estrogen was associated with decreased ionized magnesium, and an increase in serum progesterone was associated with an increase in the Ca^{2+}/Mg^{2+} ratio [50]. Additionally, while it is well known that OCPs increase the risk of venous thromboembolism in patients, recent studies have shown that women with PCOS on OCPs are at a further increased risk for venous thromboembolism [51]. The relationship of increased VTE risk to magnesium deficiency in women with PCOS should be explored.

6. Endometriosis

Magnesium can also be explored in its relation to endometriosis. Endometriosis has an inflammatory component, and as discussed above, magnesium is involved in inflammatory processes. Magnesium also has a role in relaxing smooth muscle [52]. Magnesium intake from food sources has been found to have an inverse relationship

with endometriosis [53]. One study found no difference in levels of total and ionized magnesium in endometriosis vs. control patients, though it was noted that participants in this study were taking various vitamin supplements [54]. Further studies are necessary to explore the role of magnesium in endometriosis further.

7. Gynecological Surgery

Magnesium can also serve an important role in preventing thromboembolic events in patients after gynecological surgery. Magnesium sulfate has been shown in *in vivo* experiments to reduce mortality in induced acute thromboembolismin mice [55]. It has been shown that after cholecystectomy, higher levels of magnesium were found in patients who did not develop thrombosis of the lower limbs compared to those who did [56]. The role of magnesium in preventing thromboembolic events in patients after gynecological surgery has not yet been explored, but perhaps would show similar results.

8. Cancer

Magnesium plays an interesting role in cancer, not only due to the association with inflammation discussed, but also due to its role in the cell cycle and proliferation, as discussed above [57]. Magnesium is needed to maintain genomic stability by stabilizing DNA and chromatin, regulating cell proliferation, and act as an enzymatic cofactor for DNA processing and removal of regions of DNA damage [58] [59]. Therefore, hypomagnesemia could potentially lead to increasing DNA mutations and unregulated cell cycling. Magnesium has also been linked to increased oxidative stress [60].

Decreased dietary intake of magnesium has been linked to various cancers. High magnesium concentration in drinking water has been linked to lower death rates of breast, prostate, and ovarian cancers [61]-[63]. In addition, an increased intake of magnesium is associated with a decreased risk of colorectal cancer in women [64] [65]. Interestingly, magnesium has been found to modify the effects of certain nitrates in drinking water on the development of colon cancer; colon cancer is linked to high nitrate levels in drinking water [66]. This may be due to the fact that low dietary intake of magnesium is associated with poor DNA repair capacity [67]. An increased Ca^{2+}/Mg^{2+} ratio could also have consequences in cancer development in addition to cardiovascular effects. It has been suggested that an increased ratio could even potentially lead to increased risk for postmenopausal breast cancer [68].

Additionally, hypomagnesemia is frequently seen in cancer patients, often in the terminal stages [69]. Decreased dietary intake, GI losses, urinary losses due to medications, chemotherapy, and intrinsic causes due to malignancy itself may be causes of this [70]. Hypomagnesia is associated with increased mortality rates in hospitalized patients [71].

Elderly patients or patients with kidney disease can't handle ingested magnesium as well, resulting in hypermagnesemia. Side effects of high magnesium levels include nausea, vomiting, lethargy, low blood pressure, low pulse rate, difficulty breathing, and in extreme cases, coma and death. Even in younger patients with normal kidneys, magnesium sulfate should not be used at a dose of more than 10 gm per day or for more than one week without a doctor's supervision [72].

9. Conclusion

Magnesium is extremely relevant to women's health issues, with more knowledge yet to come on the relationship between magnesium and gynecology. The levels of magnesium vary throughout the menstrual cycle and are closely related to the levels of calcium. This is extremely relevant to women, for the ratio of Ca^{2+}/Mg^{2+} can affect cardiovascular event risk, venous thromboembolism risk, and possibly even PCOS. The contributions of magnesium to the field of women's health are far reaching, spanning effects on PMS to menopause. Magnesium supplementation has shown promise in treating PMS and menstrual migraines, hot flashes, and even decreasing breast and ovarian cancer risk. The effects of magnesium deficiency on other gynecological conditions, such as fibroids, uterine polyps, and pelvic inflammatory disease have not yet been thoroughly explored, though could show promising contributions.

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Appendix

Magnesium Ion Chemical Formula [73].

Chemical Names: Magnesium ion; Magnesium (2+); Magnesium cation; Magnesium ions; Magnesium, ion (Mg^{2+}); Mg^{++};

Molecular Formula: Mg^{2+}.

Molecular Weight: 24.305 g/mol.