Serum Magnesium Concentration in premenopausal, menopausal Women, during normal and EPH-Gestosis Pregnancy and the Effect of diuretic Therapy in EPH-Gestosis*

G. Ajayi

Zusammenfassung

Serum-Magnesium-Spiegel wurden bei schwangeren Frauen während normaler Schwangerschaft (I, II, III Trimenon), im III. Trimenon bei EPH-Gestose und bei Frauen vor und während der Menopause gemessen. Die Wirkung von verschiedenen Diuretika-Therapien (Dichlotride (Chlorothiazid), Arumil (Amilorid-HCL), Moduretik (Amilorid-HCL plus Chlorothiazid) und Modukrine (Amilorid-HCL plus Chlorothiazid plus Timololmalerat)) auf den Serum-Magnesium-Spiegel bei EPH-Gestose wurde eine Woche nach Behandlungsbeginn untersucht. Bei normal verlaufender Schwangerschaft sanken die Serum-Magnesium-Spiegel mit fortschreitender Schwangerschaftsdauer. Die Serum-Magnesium-Spiegel der Patientinnen, die allein mit Thiazid-Diuretika behandelt wurden, waren niedriger als in den Kontrollgruppen. Die Serum-Magnesium-Spiegel in der Menopause-Gruppe waren signifikant höher als in der Gruppe der Frauen vor der Menopause. Diese Studie zeigt, daß die Verwendung von Kalium-sparenden und Magnesium-sparenden Diuretika theoretisch eine Möglichkeit bietet, die negativen Wirkungen herkömmlicher Diuretika auf den Elektrolythaushalt bei EPH-Gestose zu vermeiden. Es wurden nur Schwangere mit EPH-Gestose-Komplex in dieser Studie aufgenommen.

Summary

Serum magnesium levels were measured in pregnant women during normal pregnancy (I, II, III trimester), third trimester-EPH-Gestosis women, premenopausal and menopausal women. The effect of different diuretic therapy (Dichlotride (Chlorothiazid), Arumil (Amilorid-HCL), Moduretic (Amilorid-HCL plus Chlorothiazid) and Moducrine (Amilorid-HCL plus Chlorothiazid plus Timololmalerate)) in EPH-Gestosis on serum magnesium levels after one week of treatment were studied. During normal pregnancy serum magnesium level decreased with advancing gestational age. Serum magnesium levels of patients treated with thiazide diuretic alone were found to be lower than in the control groups. Serum magnesium levels in the menopausal group were significantly higher than in the premenopausal group. This study shows that the use of potassium sparing and magnesium sparing diuretics theoretically offers possibility to avoid the negative effects of electrolyte balance of conventional diuretics in EPH-Gestosis. Only pregnant women with EPH-Gestosis complex were used in this study.

Résumé

Des taux sériques de magnésium sont été mesuré chez des femmes enceintes durant la gestation normale (I, II, III triménon), dans le 3ième triménon avec gestation EPH et chez des femmes avant et durant la ménopause.
L'effet de différents traitements diurétiques (Dichlotride (Chlorothiazide), Arumil (Amilorid-HCL), Moduretik (Amilorid-HCL + Chlorothiazid) und Modukrine (Amilorid HCL + Chlorthiazide + Timololmalerat)) sur le taux sérique de Magnésium chez la gestation EPH une semaine après le commencement du traitement, a été observé.
En cas de grossesse normale, les taux sériques de magnésium ont diminués avec durance, en progression de la gestation. Les taux sériques de magnésium des patientes qui sont étées traitées seulement avec des diurétiques-thiazides, étaient plus bas que chez les controles. Les taux sériques de magnésium étaient significativement plus hauts dans le groupe des femmes en ménopause que cels des femmes avant la ménopause.
Cette étude démontre, que l'usage des diurétiques épargnants du potassium et du magnésium offre théoretiquement une possibilité pour éviter les effets négatives des diurétiques traditionnels sur l'équilibre des électrolytes chez la gestation EPH.
Que des femmes enceintes avec le complex de gestation EPH ont été admis dans cette étude.

Introduction

It is established that thiazides and loop diuretics increase the urinary excretion of magnesium [8, 13, 20]. There are evidence to support the fact that diuretics like Amiloride are not magnesiumretic [24, 40], and they lead to a reduction in magnesium urinary excretion [12, 14]. Recently Moduretic (a fixed combination of Amilorid and Hydrochlorothiazide) has been shown to increase the level of potassium and magnesium content in skeletmuscle significantly [15]. Reduction in tissue magnesium levels result in reduced intracellular potassium concentrations, provided other determinants of potassium equilibrum potentials remain constant [27]. If in addition the serum potassium level is reduced intracellular potassium concentration will be further decreased.
A significant negative correlation between urinary magnesium excretion during pregnancy and the increase in mean arterial pressure

Dept. of Obstetrics and Gynaecology, US Medical Center, 6790 Landstuhl, FRG
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[8], has been demonstrated. Magnesium deficiency is a factor in placenta insufficiency, which lead to latent blood pressure rise, fetal hypotrophy, premature contraction and cervix insufficiency [10]. Recently, evidence that magnesium deficiency could be a causal factor of EPH-Gestosis has been discussed [10].

In this study, we report the concentrations of magnesium measured in serum of normal pregnant women at different gestational age, non pregnant women, and EPH-Gestosis women before and after short-term diuretic treatment, premenopausal and menopausal women since serum magnesium level is said to be the quickest, simplest and most reliable method of initially evaluating a state of magnesium deficiency [25], and a low serum magnesium usually signifies depletion of the whole body stores [16], although some reports consider it unreliable [17, 30, 35].

Methods and Material

Serum concentrations of magnesium were measured using atomic absorption spectrophotometry in peripheral blood in the following groups of women: Group I consisted of n = 57 healthy patients with normal pregnancies between 3rd and 40th weeks of gestation (primigravidae et multigravideae), Group II consisted of n = 10 non pregnant normal menstruating women (18 – 33 years old) and in Group III were n = 23 women with EPH-Gestosis before the beginning of a week's treatment with different diuretics (Dichlotrid (n = 5) 2 × 1 (50 mg); Arumil (n = 7) 2 × 1 (5 mg); Moduretic (n = 6) 2 × 1 and Moducrine (n = 6) 2 × 1 tablets daily (MSD-Sharp Dohme, München/Germany) and after treatment. Group IV consisted of n = 10 premenopausal (42 – 46 years old) and n = 10 menopausal women (58 – 70 years old). Routine statistical analysis using Student t-Test, Wilcoxon test and non parametric analysis (Kruskal Wallis (1-way Anova =) U-Test) were used. Our normal laboratory serum magnesium level lies between 0.70 – 1.00 mmol/l. Only pregnant women with EPH-Gestosis complex were used in this study.

Results

Fig. 1 shows the mean serum concentration of magnesium (Mg^{2+}) in maternal blood throughout human gestation starting from the 3rd week of pregnancy (n = 8/0.84 ± 0.03 mmol/l mean ± SD). A significant reduction in serum concentration of magnesium was found starting from 17 – 20 week of gestation reaching the lowest level at 25 – 28th week of gestation (0.80 ± 0.03/0.72 ± 0.03 mmol/l mean ± SD) and thereafter, slowly rising but not reaching the level at the beginning (8 – 12th week of gestation = 0.82 ± 0.04 mmol/l mean ± SD) at the end of pregnancy (37 – 40th week of gestation = 0.77 ± 0.03 mmol/l mean ± SD). The mean serum magnesium concentration in normal menstruating non pregnant women (n = 10) (0.94 ± 0.03 mmol/l mean ± SD) is significantly higher than any value during pregnancy ($p < 0.01$) (Fig. 1). Significantly ($p < 0.01$) lower values were found in third trimester EPH-Gestosis patients (n = 24/ 0.71 ± 0.03 mmol/l mean ± SD) when compared to values of women with normal pregnancy (n = 24/0.75 ± 0.03 mmol/l ± SD) at the same gestational age before treatment with diuretics.

Fig. 2 shows mean concentrations of magnesium in EPH-Gestosis group before and after treatment with Dichlotrid (Thiazide n = 5) 0.73 ± 0.02m ± SD/0,70 ± 0.03 mmol/l m ± SD $p < 0.05$;

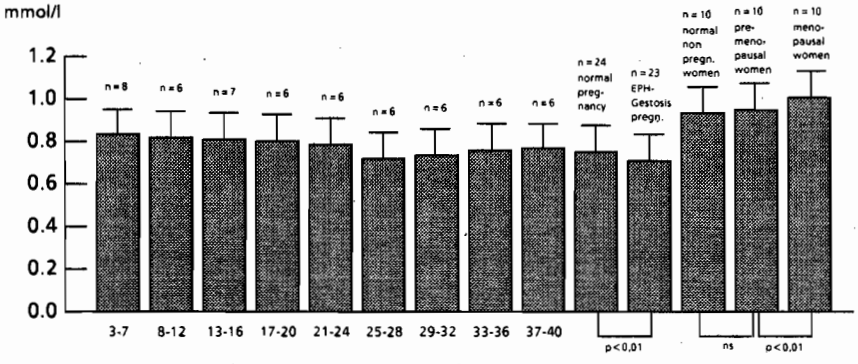

Fig. 1: Serum magnesium concentration during normal, EPH-Gestois pregnancy in premenopausal and menopausal women.

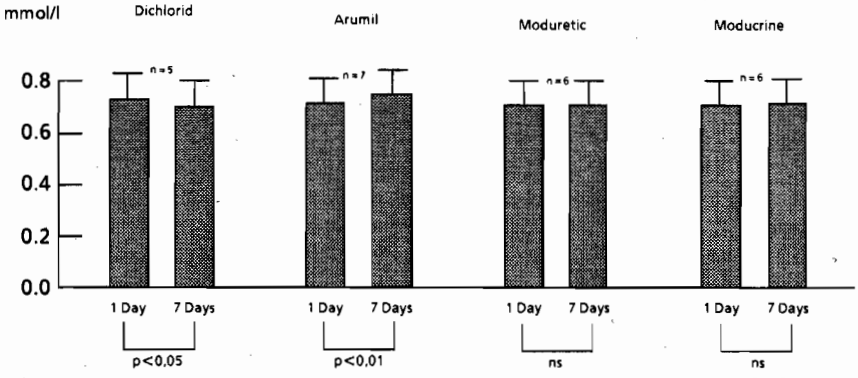

Fig. 2: Mean serum levels of magnesium in 1 week EPH-Gestois before and after therapy with Diuretic.

Arumil (Amilorid-HCL n=7) 0.72±0.03 mmol/l m±SD/ 0.75±0.03 mmol/l m±SD; Moduretic(Hydrochlorothiazid + Amilorid-HCL n=6) 0.71±0.03 mmol/l m±SD/0.72±0.04 mmol/l m±SD and Moducrine (Hydrochlorothiazid + Amilorid-HCL + Timololmalerate n=6) 0.71±0.04 mmol/l m±SD/0.71±0.04 mmol/l m±SD. The serum magnesium levels of patients treated with thiazide diuretic alone were found to be lower after treatment than in the other groups. No positive or negative correlation could be demonstrated between serum concentration of magnesium and advancing gestational age. No signs or symptoms of hypomagnesiemia were seen in those patients with low serum magnesium during normal pregnancy. Significantly higher serum magnesium level were found in the menopausal group (n=10/1.01±0.03 mmol/l mean ±SD) than in the premenopausal group n=10/0.95±0.04 mmol/l mean ±SD) ($p<0.01$) (Fig. 1).

Discussion

The reduced serum level of magnesium found during pregnancy in our study confirms the findings of other authors [7, 25]. The lowest level was found in the 25–28th gestational week in our study. The magnesium demand is increased during the process of body growth, tissuerepair, stress, diet imbalances and through environmental factor. High demand for magnesium during pregnancy and adolescent has been reported [41, 42] being an explanation for the declined level found during the course of normal pregnancy. Because in several EPH-Gestosis cases, a high incidence of low serum levels of magnesium has been found, a causal-relationship between magnesium deficiency and Gestosis [7, 25] has been proposed. In our study, lower levels of magnesium were found in EPH-Gestosis patients than in normal third trimester pregnant women. The high incidence of lower serum magnesium level found in EPH-Gestosis could be explained through secondary effect or respective catecholamine induced effect [38, 39]. This cannot be proved alone with serum level. The evolution of magnesium deficiency may be of clinical importance because of its influence on potassium metabolism. Magnesium deficiency may result in lowering of the intracellular potassium content, and potassium supplementation should not rectify this, as potassium cannot be transported into cell in sufficient amounts. Magnesium deficiency is a recognised complication of diuretic therapy. The thiazides ammonium chloride, and furosemide have specifically been implicated [19, 21, 23, 31, 32, 34, 44, 46, 48]. Aldosterone antagonists have been shown to decrease renal excretion of magnesium [11], this may be therapeutically important [22].

The major finding, in our study, was that Dichlotride therapy for one week alone, produced significantly lowering effect on serum magnesium. This biochemical abnormality was not observed in other groups treated with Arumil, Moduretic and Moducrine. These findings further confirm our previous reports and those of others [1, 2, 28, 36, 45]. Such changes could be associated with a decrease intracellular magnesium, leading in turn to a diminution in intracellular potassium. Intracellular potassium levels may remain low in presence of intracellular magnesium depletion. The effects of magnesium supplementation on intracellular potassium levels during diuretic therapy have not been adequately described, although such therapy would be theoretically correct, and it has been demonstrated that, acutely, magnesium infusions increase intracellular potassium. Although the diuretic therapy in EPH-Gestosis has been questioned in the recent years by several authors, those of potassium sparing and magnesium sparing diuretic (Amiloride, Spirolactone and Triamteren) theoretically offers a possibility to avoid the negative effects on electrolytes balance of conventional diuretics [1, 2, 3]. The detection of whole body magnesium deficiency by means of serum levels is somewhat comparable to reliance on the serum potassium as an index of total body potassium status. The alternatives of measuring red cell or skeletal muscle magnesium and complicated infusion and balance techniques, cannot be considered as every day procedures. The reference range for magnesium remains to be well defined, though recognised as narrow, and it has been said that values at the lower limit of the range should not be accepted uncritically as normal [45]. Thyrocalcitonin is known to decrease renal excretion of magnesium through an increased reabsorption of this cation at the ascending limp of the loop of *Henle* [37], and would then tend to raise serum magnesium levels. Therefore, the decrease in serum magnesium observed at the end of the 1 week of therapy should not be expected. However, such a decrease also occurs with loop diuretics that increase calcium excretion and are supposed consequently to decrease thyrocalcitonin secretion [28]. The renal loss of magnesium provoked by diuretics therefore does not appear to be related to the altered renal handling of calcium induced by these drugs. It is known that patients with essential hypertension have comparatively high levels of parathyroid hormone [26]. Lower levels of estrogens may be

associated with diminished uteroplacental perfusion. Pregnancies complicated by essential hypertension may be associated with a diminished production of estrogen [4, 5, 6]. Because estrogens are known to be inhibitor of bone resorptive effects of parathyroid-hormone, any decrease in estrogen might be expected to diminish the expected compensatory increased levels of parathyroid hormone. Hypomagnesemia is well known to suppress the secretion of parathyroid hormone. In our study lower maternal serum levels of magnesium were observed. A recent report from *Barnea* and *Naftolin* [9] has documented decreased activities of vasoactive enzymes, such as catechol-ortho methyl transferase and monoamine oxidase, in placentas from pregnancies complicated by severe hypertension, and these enzymes require magnesium as cofactor. No data are currently available on other tissue levels of magnesium in essential hypertension during pregnancy.

Our results further support the view that pregnancy induces a low-magnesium syndrom, which is being potentiated, in several cases through the EPH-Gestosis. The clinical use of potassium sparing and magnesium sparing diuretics theoretically offers a possibility to avoid the negative effect on electrolytes balance of conventional diuretics in EPH-Gestosis. In view of the limited results, further investigations on this line are needed.

In our study, serum magnesium levels in the menopausal group were significantly higher than in the premenopausal group; supporting the reports of *Lindsay* et. al. 1980 [29] and *McNair* et. al. 1984 [33] who observed elevated serum magnesium level in menopausal patients. The magnesium excess is believed to be derived from bone [29].

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Author: Dr. *G. Ajayi,* Arzt für Frauenheilkunde und Geburtshilfe, Münsterstr. 344, D-4000 Düsseldorf 30, FRG