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Serum and intracellular magnesium during normal pregnancy and in patients with pre-eclampsia

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ABSTRACT

Objective To determine the serum and lymphocyte magnesium concentrations during normal pregnancy and to compare the magnesium status in the third trimester of pregnancy between women with normal pregnancy and those with gestational hypertension (GH) or pre-eclampsia (PE).

Design A prospective cross-sectional study followed by a prospective comparative study.

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Subjects Seventy-one healthy pregnant women, with normal pregnancies between 6 and 38 weeks gestation. The second part included 43 women in the third trimester of pregnancy, 11 had GH, 11 had PE and 21 formed the comparison group of healthy normotensive women.

Main outcome measures Total serum and intralymphocytic Mg concentrations and urinary Mg excretion.

Results There was a progressive reduction in total serum magnesium concentrations during normal pregnancy, thought to be partly due to haemodilution, because the decline in concentration of serum proteins paralleled that of Mg ($P<0{\cdot}001$). In the three groups studied in the third trimester the serum Mg concentration was very similar in the GH and the comparison groups, but it was significantly higher in the PE group ($P<0{\cdot}01$). The intralymphocytic Mg concentrations and the urinary Mg excretion were similar in all three groups. In five patients treated with MgSO4 there was a large increase in the serum Mg concentration and in the urinary Mg excretion. The intralyphocytic Mg concentration remained remarkably stable.

Conclusions Our data does not support the conclusion that Mg deficiency is the primary cause of pre-eclampsia.

Pre-eclampsia is a frequent complication of pregnancy and occurs in approximately 5–7% of pregnancies in Europe and the United States of America (Burrow & Ferris 1988; Pritchard *et al.* 1985).

The pathophysiological mechanism in pre-eclampsia is characterized by constriction of arterioles, leading to increased peripheral resistance and resulting in arterial hypertension. This vasospasm is associated with endothelial damage leading to platelet aggregation and fibrin deposits in the arterioles of various susceptible organs, which explains the multiplicity of clinical features and laboratory abnormalities. Despite intensive research during the past few decades, the cause of pre-eclampsia remains unknown. Recent medical investigations suggest that magnesium (Mg) deficiency could play an important role in the pathogenesis of pre-eclampsia, particularly in regulating the tonus of arterioles and veins (Seelig 1980; Altura *et al.* 1983; 1984; Conradt *et al.* 1984b; Günther 1985; Watson *et al.* 1986). Mg is primarily an intracellular cation and it is known that the extracellular Mg does not reflect the state of Mg balance, therefore Mg concentration was measured in the serum and in lymphocytes. The purpose of this study was to measure serum and intralymphocytic concentrations of Mg during normal pregnancy and to compare serum and intracellular Mg concentrations between women with hypertension in pregnancy and a comparison group of normal pregnancies.

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Subjects and methods

The first part of the study lasted 1 year and included 71 healthy pregnant women, aged 19–43 years with normal pregnancies between 6 and 38 weeks gestation. Women with essential hypertension, or who previously received Mg or diuretics and women with a previous history of renal disease were excluded. The second part of the study lasted also 12 months and involved 22 patients with hypertension according to the following criteria. Gestational hypertension (GH) was defined as a blood pressure of $\geq$140–90 mmHg, measured in the upper arm in the left lateral recumbent position in two or more occa-

Table 1. Characteristics of the women in the three study groups

Variable	Gestational hypertension (n = 11)	Pre-eclampsia (n = 11)	Normotensive (n = 21)
Age (years)	27·5 (6·6)	28·5 (4·6)	28·5 (4·6)
Gestational age (weeks)	37·2 (2·2)	35·2 (2·3)	36·2 (0)
Primiparous (%)	100	91	43
Blood pressure (mm Hg)			
Systolic	145 (6·6)	160 (9·9)	118 (9·1)
Diastolic	100 (6·6)	107 (6·6)	75 (4·6)
Proteinuria (g/24 h)	0,13 (0·07)	2·7 (2·3)	–
Haematocrit (%)	38·8 (2·3)	39·0 (3·6)	36 (2·3)

Data are mean (SD).

sions at 6 h intervals. Pre-eclampsia (PE) was defined as hypertension and proteinuria ≥300 mg/24 h, or >1 g/l in a random urine specimen. HELLP syndrome was diagnosed if there was evidence of haemolysis, elevated liver enzymes and a platelet count less than 100×10^9/l. All the hypertensive patients were admitted to the obstetric unit of the University Hospital of Geneva, Switzerland. They were studied between 32 and 40 weeks gestation. Of the 22 patients 11 had GH and the other 11 had PE. One patient in each group developed HELLP syndrome. In the PE group, two patients had gestational diabetes mellitus. A comparison group was selected in the last 3 months of our study comprising 21 healthy women with normal pregnancy who were attending the antenatal clinic for the first time in the third trimester, they had no history of essential hypertension, renal disease or ingestion of Mg or diuretics. All these women had normal pregnancies until delivery. Table I summarizes the characteristics of the three different groups. All the women in the study had a physical examination, ultrasound scan and antenatal fetal heart rate monitoring. All patients with hypertension (GH and PE) remained in hospital and had blood pressure, reflexes, proteinuria and fetal heart rate recorded twice daily. Some of them had an anmiocentesis to determine the lecithin: sphyngomyelin ratio. Induction of *labour* was performed if fetal lung maturity was confirmed in patients with increasing blood pressure and proteinuria. Where the patient's condition improved, blood pressure, reflexes, proteinuria and fetal heart rate monitoring were reviewed weekly until term. Patients with severe PE (diastolic blood pressure ≥110 mmHg and with abnormal neurological signs) were treated with magnesium sulphate as described by Pritchard *et al.* (1985) except that we began with 2 g given intravenously and 10 g intramuscularly, but we did not systematically repeat the 5 g injection every 4 h. Intravenous hydralazine was also given, first as a bolus of 6·25 mg and than as a continuous infusion of 2·5 mg/h to a maximum of 15 mg/h. Labour was induced with oxytocin if the cervix was favourable; if the cervix was unfavourable delivery was by caesarean section.

On admission to hospital, venous blood samples were taken to measure intralymphocytic Mg concentration and plasma concentrations of Mg, sodium, potassium, calcium, creatinine, urea nitrogen, total protein, liver enzymes, haemoglobin and fibrinogen. The haematocrit, leucocyte count, platelet count, prothrombin time and partial thromboplastin time were also determined. Twenty-four hour urine specimens were collected for estimation of proteinuria, creatinine clearance and sodium, potassium and calcium excretion. Serum, lymphocytic and urinary Mg levels were measured during and after $MgSO_4$ treatment in the patients with severe PE. The same investigations were made in the 21 normal pregnant women at a comparable age of gestation.

Intracellular Mg concentrations were measured in lymphocytes as described by Elin & Johnson (1982) and modified by Girardin & Paunier (1985), within 2 h of sampling and expressed in relation to cell protein content. Plasma Mg concentrations were determined by atomic absorption spectrophotometry. Data analysis used the Mann Whitney U-test. P values of <0·05 were considered significant.

Results

Normal pregnancy

The pregnancies of all 71 women in this group progressed

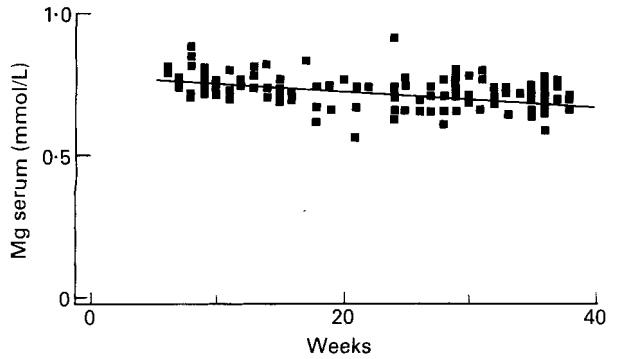

Fig. 1. Serum magnesium (Mg) concentrations in 71 normal pregnancies between 6 and 38 weeks gestation.

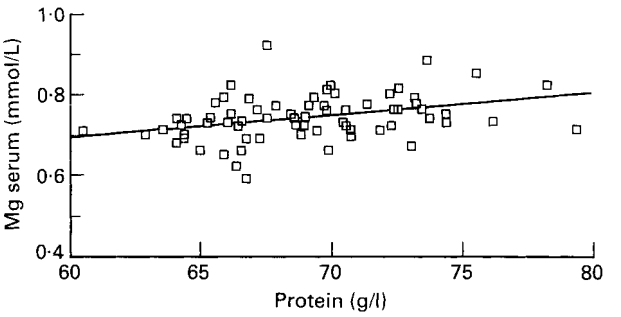

Fig. 2. Correlation between serum protein and magnesium concentrations in 71 normal pregnancies. r = 0·382, P = 0·001.

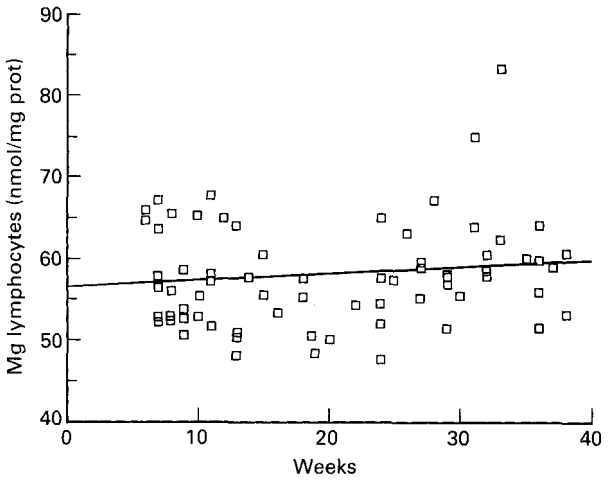

Fig. 3. Lymphocyte magnesium concentration in 71 normal pregnancies between 6 and 38 weeks gestation. $r = 0{\cdot}135$, $P = 0{\cdot}26$.

normally without development of hypertension. Fig. 1 depicts the serum Mg concentration in these women showing a gradual, small but significant decrease during pregnancy ($r = 0{\cdot}384$, $P<0{\cdot}001$). There was a significant correlation ($r = 0{\cdot}382$, $P = 0{\cdot}001$)) between serum protein and Mg concentration (Fig. 2). Fig. 3 shows the intracellular lymphocyte Mg concentration ($r = 0{\cdot}135$, $P = 0{\cdot}26$).

Hypertensive groups and comparison group

Table 2 summarizes the mode of delivery and outcome in the three study groups. As expected, there were more instrumental vaginal deliveries and caesarean sections and more small-for-gestational age infants in the GH and PE groups.

Table 3 shows that serum concentrations of Mg were very similar in the normotensive comparison and GH groups but significantly higher ($P<0{\cdot}01$) in the PE group. In contrast, the Mg concentration within the lymphocytes was similar in all three groups. Likewise, the urinary Mg excretion did not differ significantly between the three groups.

In the five patients treated with parenteral $MgSO_4$ a large increase in the serum Mg concentration and of the urinary Mg excretion was observed. However, the intralymphocytic Mg concentration remained remarkably stable (Fig. 4).

Discussion

In recent years there have been several studies of Mg metabolism during pregnancy and some have concluded that Mg deficiency might play a role in the aetiology of pre-eclampsia

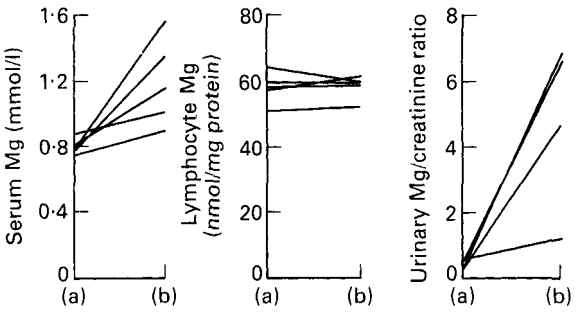

Fig. 4. Serum and lymphocyte Mg concentrations and urinary Mg excretion in five patients treated with $MgSO_4$. (a) before treatment with $MgSO_4$. (b) during treatment with $MgSO_4$.

(Seelig 1980; Altura *et al.* 1983; 1984; Conradt *et al.* 1984b; Günther 1985).

The daily intake of Mg in the diet of pregnant women has been investigated and some studies have shown that the average total intake of Mg in pregnancy in the United States amounts to only 35%–60% of the recommended 450 mg (Ashe *et al.* 1979; Franz 1987). This finding and the hypothesis that Mg deficiency could play a role in the pathogenesis of pre-eclampsia have led to controversy about whether Mg supplements should be prescribed during pregnancy. Some obstetricians routinely prescribe preparations containing from 10 to 20 mmol of Mg to be taken daily by pregnant women (Franz 1987; Conradt *et al.* 1984b).

In the first part of our study, we found a significant progressive reduction ($P<0{\cdot}001$) in serum Mg concentrations during normal pregnancy (Fig. 1) as other studies have shown (Dancis 1971; Stanton 1987). The significant correlation ($P<0{\cdot}001$) between the concentrations of Mg and proteins suggests that this decrease is partly due to haemodilution. The stability of intracellular Mg in the 71 healthy pregnant women is an argument against a state of Mg deficiency during normal pregnancy.

Animal studies (Altura *et al.* 1984) or studies of human umbilical vessels (Watson *et al.* 1986) have shown that Mg is necessary to maintain a normal vascular tonus. Rats exposed to a poor Mg diet, or entirely without Mg, develop arterial hypertension. Mesenteric circulation in these animals diminishes in proportion to the Mg deficiency (Altura *et al* 1984). Pregnant ewes deprived of Mg during gestation develop a reduction in serum Mg accompanied by arterial hypertension, retarded intrauterine growth and pathological renal and placental changes similar to those of pre-eclampsia (Weaver 1986). The sudden fall in extracellular Mg produces a rapid increase in the tonus of umbilical arteries and veins taken from normal fetuses

Table 2. Mode of delivery and outcome in the three study groups

Mode of delivery	Gestational hypertension ($n = 11$) n (%)	Pre-eclampsia ($n = 11$) n (%)	Normotensive ($n = 21$) n (%)
Instrumental vaginal delivery	4 (36)	3 (27)	2 (10)
Caesarean section	2 (18)	6 (55)	1 (5)
Small for gestational age (<10th centile)	3 (27)	3 (27)	1* (5)

*At the 10th centile.

Table 3. Serum magnesium concentration, lymphocyte magnesium concentration and urinary magnesium excretion in the three study groups

	Gestational hypertension (n = 11)	Pre-eclampsia (n = 11)	Normotensive (n = 21)	P^1	P^2	P^3
Serum Mg (mmol/l)	0·684	0·778	0·704	0·176	0·008	0·005
Lymphocyte Mg (mmol/mg protein)	59·89	59·97	57·33	0·237	0·234	0·888
Urinary Mg (Mg/creatinine ratio)	0·42	0·45	0·35	0·272	0·538	0·888

P^1, normotensive *vs* gestational hypertension.
P^2, normotensive *vs* pre-eclampsia.
P^3, gestational hypertension *vs* pre-eclampsia.

(Altura 1983). Conversely, high dose of extracellular Mg (3 mmol/l) increase the production of vasodilating prostaglandin $F_{2\alpha}$ by endothelial cells in human umbilical veins (Watson *et al.* 1986).

We are not aware of any clinical study demonstrating that pregnant women with gestational hypertension or pre-eclampsia have a measurable Mg deficiency. Conradt *et al.* (1984b) suggested that gestational hypertension and pre-eclampsia are probably due to a Mg deficiency, they based their hypothesis on a retrospective study in which 2% of the women who had not received tocolytic drugs or Mg supplementation developed pre-eclampsia whereas none of the women who received tocolytic drugs and Mg supplementation developed gestational hypertension or pre-eclampsia. It should be noted that the women were not allocated on a random basis and there was no mention of measurement of either serum or intracellular Mg concentration. However, two prospective studies (Spätling & Spätling 1988; Sibaï *et al.* 1989) compared groups of pregnant women who received, respectively, 15 mmol and 365 mg Mg daily with control groups (who received no treatment) and found no significant difference in the occurrence of gestational hypertension and pre-eclampsia.

In our study the intralymphocytic Mg concentrations were similar in all three groups, in agreement with two other studies (Ryzen *et al.* 1987; Boston *et al.* 1989) which compared normal pregnant women with patients who had gestational hypertension or pre-eclampsia. We found that serum Mg concentrations were almost identical in the GH and normotensive groups and significantly higher in the PE group. We have no explanation for this difference. The urinary Mg excretion was not significantly different between the three groups. This is at variance with the report by Franz (1982) who found a significant negative correlation between urinary Mg excretion and the mean increase in arterial pressure in pregnant women with urinary Mg excretion less than 7 meq/g of creatinine. Finally, the stability of the intralymphocytic Mg concentrations in patients treated with high doses of intravenous $MgSO_4$ represents a powerful argument against the hypothetical deficiency of Mg in pre-eclamptic patients.

$MgSO_4$, given in high doses, is considered by some to be the first choice for treatment of severe pre-eclampsia and eclampsia (Pritchard *et al.* 1985; Lindheimer & Katz 1986) but its mode of action is not well understood and Pritchard does not consider it an effective treatment of the hypertension in pre-eclampsia. Our data do not support the hypothesis that Mg deficiency is a contributing cause of pre-eclampsia.

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