MAGNESIUM IN HEALTH AND DISEASE

Proceedings of the 2nd International Symposium on Magnesium
Montreal, Quebec, May 30-June 1, 1976

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SP MEDICAL & SCIENTIFIC BOOKS
New York • London

Influence of Parenteral Administration of Magnesium Sulfate to Normal Pregnant and to Pre-Eclamptic Women

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INTRODUCTION

The parenteral administration of magnesium sulfate ($MgSO_4$) has long been recommended for the treatment of pre-eclampsia and eclampsia (Lazard, 1925; McNeile and Vruwink, 1926). Some rely on its intravenous (i.v.) administration (Lazard, 1933; McNeile, 1934; Winkler et al., 1942; Hutchinson et al., 1963; Zuspan and Ward 1964, 1965; Zuspan, 1966; Harbert et al., 1968; Zuspan, 1969). Others prefer i.v. plus intramuscular (i.m.) injections (Pritchard, 1955; Flowers et al., 1962; Flowers, 1965, 1975; present study) for control of pre-eclampsia and reductions in maternal and infant mortality rates. Although hypomagnesemia of eclampsia has been recognized almost as long as $MgSO_4$ has been used in its treatment (Hirschfelder and Haury, 1934; Haury and Canatarow, 1942; Hall, 1957; Achari et al., 1961; Flowers et al., 1962; Flowers, 1965), few have seriously considered the possibility that Mg depletion may be contributary to the disease (McGanity, 1965; Lim et al., 1969; Seelig, 1971; Seelig and Bunce, 1972). One explanation may be the frequently seen hypomagnesemia during normal pregnancy, particularly during the final months when it may be even lower than in pre-eclampsia or eclampsia (Bogert and Plass, 1923; Watchorn and McCance, 1932; Zaharesco-Karaman et al., 1936; Wolff et al., 1937; Hall, 1957; Newman, 1957; Wallach et al, 1962; Lim et al., 1969(, even with correction for hemodilution (Bastos de Jorge et al., 1965).

The high doses of $MgSO_4$, required and tolerated in the treatment of pre-eclampsia and eclampsia, suggest that such therapy might be repairing a deficit, in addition to acting as a sedative and an antihypertensive agent. Our study of the effect of administration of parenteral $MgSO_4$* to pre-eclamptic and to normal pregnant women, in doses insufficient to produce hypermagnesemia, has shown retention of almost all of the injected magnesium (Mg). Following administration of the Mg, most of the patients had marginally low serum calcium (Ca) levels, obvious hypocalcemia was noted in over half of the pre-eclamptic women, and urinary phosphorus (P) output was low. We postulate that Mg insufficiency may be common during pregnancy, may contribute to parathyroid dysfunction, and may play an etiologic role in pre-eclampsia.

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*$MgSO_4 17H_2O$ contains 10% Mg^{2+} thus each gram (g) $MgSO_4$ delivers 100 mg Mg^{2+}.

METHODS

Fourteen severely pre-eclamptic women, admitted to Margaret Hague Maternity Hospital with systolic blood pressures of 150-190 mm Hg, diastolic pressures of 90-120 mm Hg, and with one or more of the following: edema, proteinuria, and hyperreflexia, had blood samples drawn for serum total protein/albumin, creatinine, electrolytes (including Ca, P, and Mg), blood urea nitrogen, (BUN) and glucose. They were immediately given 400 mg Mg as the sulfate i.v. and 400-600 mg i.m. Their 24-hr urines were collected and a second blood sample drawn. Five of the patients required additional Mg (100-900 mg i.m.) the next day; two required 400 mg i.v. and 600 mg i.m. Cerebrospinal fluid (CSF) Mg levels were obtained from eight women who were delivered surgically after spinal anesthesia. Seventeen normal pregnant women, near term, had the same blood analyses performed immediately before being given a test dose of 100 mg Mg i.m. Their blood was again drawn when the 24-hr urine collection was complete. Each infant's weight and Apgar scores at 1 and 5 min were recorded.

RESULTS

None of the pre-eclamptic patients had pretreatment blood or urine abnormalities, other than as inidcated in Figures 1-3. Their serum albumin levels were only marginally lower than were those of the normal pregnant women. Hyperreflexia, seen in all but one of the pre-eclamptic patients, was corrected on treatment with 800-2000 mg Mg (Fig. 1). The systolic blood pressures were lowered by 30-60 mm Hg; diastolic pressures were reduced to a range of 82-104 (with one dropping to 60 mm Hg) after treatment. Edema and proteinuria were also reduced in most of the patients after the therapy; in some, normal findings were observed only after delivery. Twelve of the fourteen had serum Mg levels from 1.4-1.8 mg% (1.2-1.5 meq/liter) (Fig. 2). After administration of 800-1000 mg Mg over 1-2 days, serum Mg levels remained subnormal or at the lower limits of the normal range in half the subjects the day after the treatment. All retained most of the administered Mg (Fig. 2). Hypocalcemia was marked in three, between 7.6-8.0 mg% in five, and not above 8.6 in any (Fig. 3). Serum P levels were within normal limits. The 24-hr Ca urinary excretions were normal in five, and slightly low in the rest after the Mg-therapy. All but three had urinary P outputs below normal after the Mg (Fig. 3).

Cerebrospinal fluid levels of Mg of the eight women requiring section were within narrow limits: 2.56-2.70 meq/liter, the low and high limits from patients given 2000 and 1600 mg Mg, respectively. This is in accord with the observations of Pritchard (1955), who obtained comparable levels despite high enough doses of $MgSO_4$ to produce and maintain serum levels of Mg of 3-8 meq/liter.

Serum Mg levels were generally lower among the normal pregnant women than among the pre-eclamptic patients. All were hypomagnesemic, with serum Mg levels of 1.2-1.8 mg% (1.0-1.5 meq/liter). Their 24-hr urinary Mg outputs, following 100 mg Mg i.m., were less than the amount given, or minimally more in nine of the ten women with pretreatment serum Mg levels below 1.7 mg%. Five of the seven women, whose pretreatment serum Mg levels were marginally low (1.7-1.8 mg%) excreted 57-124 mg; two excreted significantly more than they were given (Fig. 4). The serum Mg levels of the normal pregnant women rose only slightly. Four had serum Ca levels below 8.5 mg%; five had serum P values below 3 mg% before the

Mg was administered (see Fig. 5). Four of the five patients with hypophosphatemia were among the five with the highest 24-hr urinary Mg-outputs after their 100 mg dose of Mg. The 24-hr urinary output of P of the patient who excreted 310 mg Mg after the test dose, although one of the highest in this group (0.7 g P), was still subnormal.

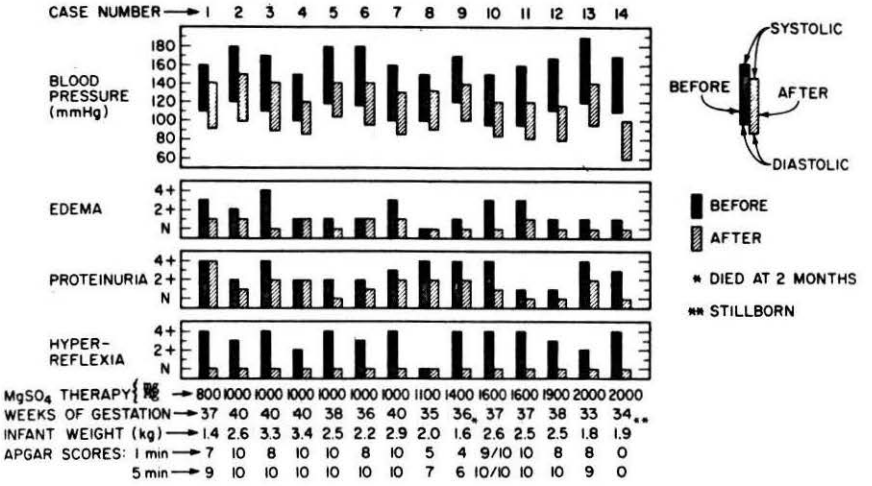

Figure 1. Clinical responses to parenteral Mg SO_4 therapy in pre-eclampsia.

Except for two infants born to pre-eclamptic mothers (one who was stillborn and one who died 2 months later*, whose Apgar scores were 4 at 1 min and 6 at 5 min), all of the infants did well. Only two additional infants (in the pre-eclamptic group) had 1-min Apgar scores below 8. All but one had 5-min Apgars of 9-10. The infants of the pre-eclamptic women tended to be somewhat small (Fig. 1).

*No autopsies were permitted.

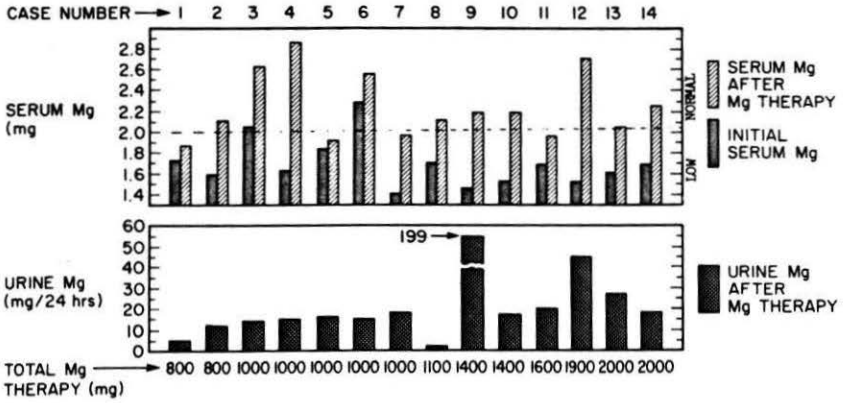

Figure 2. Mg levels in pre-eclamptic women: findings before and after $MgSO_4$ therapy.

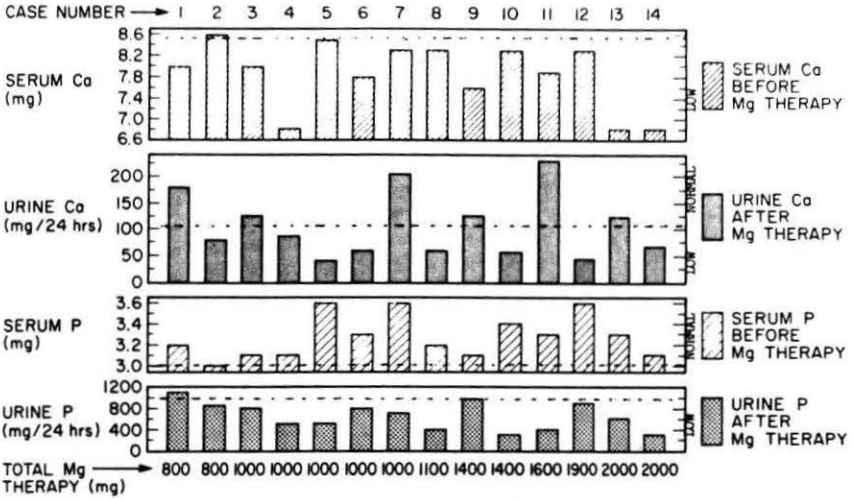

Figure 3. Ca and P levels in pre-eclamptic women: findings before and after $MgSO_4$ therapy.

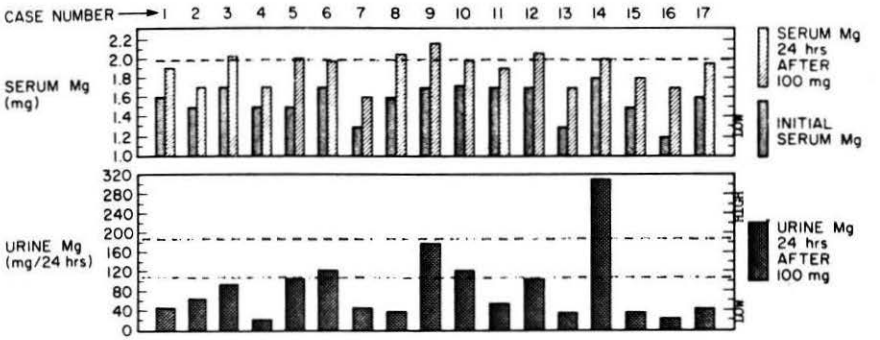

Figure 4. Mg levels in normal pregnant women near term: before and after test dose (100 mg) Mg i.m.

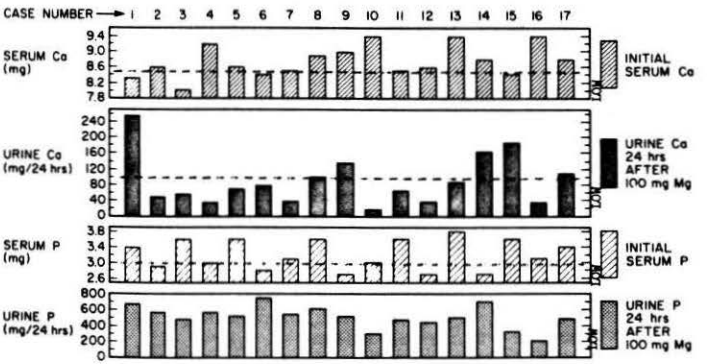

Figure 5. Ca and P levels in normal pregnant women near term: before and after test dose of Mg i.m.

DISCUSSION

In view of the retention of the 800-1000 mg Mg by the pre-eclamptic women, which did not produce higher than normal serum Mg levels 24 hr after injection nor suppression of the infants, we postulate that correction of Mg deficiency contributed to the patients' improvement. Our series included none with severe eclampsia, the control of which pharmacologic doses sufficient to maintain serum Mg levels of 4-8 meq/liter have been found necessary (Pritchard, 1955; Hall, 1957; Hutchinson et al., 1963; Flowers, 1965; Harbert et al., 1968). Our observation of somewhat higher pretreatment serum Mg levels in our pre-eclamptic rather than in our normal pregnant patients confirms the findings of Pritchard (1955) and of Hall (1957). Hall noted that toxemic women had somewhat lower plasma Mg levels than did normal pregnant women from the 12th to the 24th weeks of pregnancy; their levels rose above those of normal pregnant women towards term. The retention of the 100 mg test dose of Mg by almost all of the normal pregnant women in our series, and their subnormal serum Mg levels, suggest Mg insufficiency.

Unfortunately serum Ca and P levels were measured in only pretreatment blood specimens and the 24-hr urinary Ca and P outputs only in post-treatment specimens. The low serum Ca levels in most of the pre-eclamptic patients suggest Ca depletion, such as has evoked increased parathyroid hormone (PTH) secretion and hypophosphatemia. Their pretreatment serum P levels were within normal limits. On the other hand, chronic Mg depletion has been associated with either end-organ resistance to PTH (Estep et al., 1969; Connor et al., 1972; Woodard et al., 1972; Levi et al., 1974) or its diminished release (Suh et al., 1973; Anast, 1977). Regardless of the mechanism, Mg repletion has restored the phosphaturic response to PTH. Thus, the very low urinary excretion of P after 800-1000 mg Mg by the pre-eclamptic patients was unexpected. We had also expected high urinary P excretion in the normal pregnant women, since significant hyperparathyroidism (as measured by radioimmunoassay of PTH) frequently occurs during the last trimester of pregnancy (Cushard et al., 1972). Hypermagnesemia has suppressed PTH secretion and activity in animals (Care et al., 1966; Massry et al., 1970), as has maintenance of only slightly elevated serum Mg levels in hemodialyzed patients (Pletka et al., 1971; Freeman and Deftos, 1973). Our patients may have had transistory hypermagnesemia after their parenteral Mg that the blood specimens taken later did not disclose. Perhaps our patients had hyperparathyroidism, in the presence of hypocalcemia and hypomagnesemia, as has been described in an infant born to a mother with hyperparathyroidism (Monteleone et al., 1975). Further study of serum and urinary Mg, Ca and P, with inclusion of PTH determinations before and after Mg therapy, may resolve the seeming paradox.

Possibly, the amount of Mg given was insufficient to correct the presumed Mg deficit, even though it was adequate to control the clinical manifestations. As much as 200 mg of Mg, as the sulfate, given i.v. hourly until control of convulsions, was recommended in the early studies (Lazard, 1933; McNeile, 1934). Up to 15.4 g Mg have been given over a 5-day period, or 6-7 g Mg/24 hr, for the sedative effect, without adverse effects either to mother or infant (Pritchard, 1955; Hutchinson et al., 1963; Zuspan and Ward, 1964; Flowers, 1965; Harbert et al., 1968). In fact, fetal salvage has been improved by $MgSO_4$ therapy (Zuspan and Ward, 1965; Zuspan, 1969). Flowers suggested that the patients' tolerance of such large doses might be the result of prior depletion of tissue Mg stores. Hall (1957) suggested that Mg deficiency might contribute to eclamptic convulsions, because of their

to those of experimental Mg depletion. McGanity (1965) considered the possibility that dietary Mg deficiency might be etiologic, a possibility suggested later by Seelig (1971) and Seelig and Bunce (1972).

Young, pregnant middle-class American women have been shown to have low Mg-intakes (Johnson and Philipps, this symp.; Ashe et al, 1979), confirming the trend among college students (Seelig, 1964). Mean daily Mg losses of 40 mg were seen (Ashe et al, 1979), possibly explicatory of marginally low serum Mg, and retention of parenterally administered Mg therap Pretest serum Mg levels of all of our normal pregnant patients were below 1.5 meq/liter; seven were below 1.3 meq/liter. However, only half of the pre-eclamptic patients had serum Mg levels below 1.5 meq/liter. Interestingly, almost all of the patients, abnormal and normal, either retained most of the injected Mg or showed no significant increase in serum Mg after its administration. As for the low serum Mg of the normal pregnant women, rarely is it considered significant; it, like the common hyperparathyroidism of pregnancy, is considered physiological. Caddell et al. (1975) consider the retention of parenteral loads of Mg suggestive of deficiency: among their postpartum women given 0.4-0.5 meq/kg Mg, they found mean retention of 51% of the load. Immature multiparas and young mothers of twins retained over 90%. Eclampsia is particularly common in teen-aged pregnant girls (Zuspan, 1969), whose Mg intakes may be marginal for their own needs, apart from fetal requirements. Conceivably, maternal hyperparathyroidism (to which Mg deficit can contribute) causes neonatal hypoparathyroidism and hypomagnesemic hypocalcemia (Tsang, 1972; Unsigned Editorial, 1973), an abnormality that occurs most often in infants born of mothers with complications during pregnancy, including toxemias (Mizrahi et al., 1968; Tsang, 1972; Seelig, 1980).

Experimental Mg deficiency causes loss of Mg and potassium (K), and retention of sodium (Na) and Ca (Seelig and Haddy, 1976). Such electrolyte changes cause vasoconstriction (Haddy and Seelig, 1976). Zuspan (1969) has stressed that eclampsia involves arteriolar vasospastic disease, as well as abnormal electrolyte distribution: tissue Na retention and K loss. McCall and Sass (1956) have shown that $MgSO_4$ treatment of eclamptic patients significantly lowers their cerebral vascular resistance and increases cerebral blood flow. Weaver (This Symp.) has demonstrated that increased blood coagulability of pre-eclamptic patients is correctible by treatment with $MgSO_4$. These new findings, plus the long known neuromuscular irritability, convulsions, and renal damage of Mg deficiency, that may be reversible (Whang et al., 1973), support the premise that Mg deficiency can contribute to pre-eclampsia and eclampsia.

SUMMARY

The manifestations of pre-eclampsia of pregnancy resemble those of hypomagnesemia in that both are characterized by neuromuscular irritability and convulsions, renal damage, and often edema. Whether or not hypertension develops depends not only on the Mg deficiency, but on other dietary or hormonal abnormalities. Pharmacologic doses of parenteral Mg have long been used to control eclamptic convulsions and hypertension. Better fetal salvage has been reported with Mg therapy than with diuretics or other anti-hypertensive therapy. Retention of large amounts of administered Mg by pre-eclamptic women is common, as is the marginal to low Mg intakes and levels of normal pregnant women.

tulate that Mg deficiency may be contributory to pre-eclampsia, and that the response to Mg may reflect correction of the deficit, as well as its pharmacologic effects, serum and 24-hr urinary levels of Mg were measured in pre-eclamptic women, before and after high dosage parenteral $MgSO_4$ therapy. Cerebrospinal fluid Mg levels were measured when feasible. Serum and 24-hr urinary Mg levels were determined in normal pregnant women at term. The low levels of Mg and its greater retention in pre-eclampsia than in normal pregnant women, suggest tissue Mg depletion in toxemias of pregnancy.

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