METAL IONS IN BIOLOGICAL SYSTEMS

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The Role of Magnesium in Pregnancy, for the Newborn, and in Children's Diseases

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1. INTRODUCTION

The recent interest in the element magnesium is probably in part accidental and partly due to the development of new techniques, such as atomic absorption spectrophotometry (AAS) permitting accurate assays in biological samples. These technological advances have facilitated the correlation of laboratory results with clinical disorders.

Especially in obstetrics results have been published in recent years focussing on magnesium. Here the observation of a significant reduction of preterm delivery by magnesium supplementation during pregnancy is to be emphasized (see below) [1].

2. MAGNESIUM IN PREGNANCY

2.1. Magnesium Metabolism in Pregnancy

2.1.1. *Magnesium Concentration in Plasma, Erythrocytes, and Myometrium*

Under normal conditions, plasma concentrations of magnesium average 0.9 mmol/liter, ranging from 0.75 to 1.0 mmol/liter in 90% of cases [2,3]. Of the total body magnesium, only 55% is free [4]; the remainder is bound in a variety of complexes, mainly to albumin. Erythrocytes contain 2.30 ± 0.17 mmol/liter magnesium [5]. In uterine tissue of nonpregnant women, the magnesium concentration is even higher, 6.58 mmol/kg of moist weight [6].

Especially in the early weeks of pregnancy, a substantial decrease in plasma magnesium levels was demonstrated [7,8]. Also in our investigations, magnesium concentrations were found to be reduced from a nonpregnant value of 0.83 ± 0.05 to 0.71 ± 0.07 mol/liter in week 40 of pregnancy [9]. It is well known that dilution of plasma occurs during pregnancy and that the quantity of serum protein decreases correspondingly. Total magnesium can be corrected for total protein according to the formula [10]:

$$Mg_c = \frac{Mg_m}{0.76 + PP/30}$$

where Mg_c = corrected total magnesium (mmol/liter); Mg_m = measured total magnesium (mmol/liter); PP = measured total protein (g/dl). However, the magnitude of correction is usually small [10], and Seelig [11] reviewed the literature on this subject, concluding that pregnancy-induced hypomagnesemia is real.

During pregnancy a significant decrease of magnesium concentration in myometrium is also observed. Related to dry weight, myometrical magnesium concentrations decreased from 16.6 ± 2.5 mmol/kg to 13.3 ± 2.9 mmol/kg in the last 10 weeks of pregnancy. Related to wet weight, a reduction from 3.40 ± 0.51 to 2.82 ± 0.64 mmol/kg could be demonstrated [9].

2.1.2. *Renal Magnesium Excretion*

Urinary magnesium excretion was studied in order to find out the reason for the hypomagnesemia developing during pregnancy and correlated with diminished magnesium levels of the myometrium [12]. Twenty-four-hour urine and blood samples were taken from seven pregnant volunteers once every 2 weeks. Magnesium was determined in the urine and plasma using the atomic absorption spectrophotometry (AAS) technique. A 25% increase in magnesium excretion from 3.81 ± 0.92 to 4.78 ± 1.18 mmol/24 hr ($p < 0.02$) was shown. Simultaneously, plasma magnesium levels decreased by 15% from 0.82 ± 0.05 to 0.70 ± 0.03 mmol/liter ($p < 0.01$). Magnesium clearance increased by 41% from 3.23 ± 0.76 to 4.57 ml/min ($p < 0.01$). Hence, increased urinary magnesium excretion during pregnancy is probably one of the main reasons for the resulting magnesium deficit. As reasons for the relatively low renal reabsorption the following changes associated with pregnancy are to be considered: (1) the increase in extracellular fluid, (2) the increase in glomerular filtration rate, and (3) reduced magnesium reabsorption due to increased sodium reabsorption. In addition, the magnesium requirement is markedly increased during pregnancy [11], but we have no information as to whether the choice of nutrients may be changed, i.e., meals with low magnesium content may be preferred. Reduced food intake may also contribute to the resulting magnesium deficit.

2.2. Magnesium Supplementation During Pregnancy

2.2.1. *Effect on the Mother*

Even though magnesium has had its place in obstetrics for the management of preeclampsia and eclampsia since the beginning of this

century, its significance for preterm labor was only recognized in the 1960s [13]. Ten years later a reduction of preterm labor by low-dose magnesium infusion (1—2 g/day) was described [14]. General interest in the role of magnesium in obstetrics was reactivated by our observation that supplemental magnesium medication allowed a considerable reduction of the dose of β-adrenergic agents used for tocolysis of preterm labor [15]. Based on these findings, it could be demonstrated, mainly in retrospective studies, that the frequency of fetal growth retardation and eclampsia/preeclampsia was reduced in association with magnesium supplementation [16].

To ascertain these observations a double-blind study was performed in 568 unselected women included in the trial as early as possible in pregnancy but not later than 16 weeks into gestation. Fifteen millimoles of magnesium as the magnesium aspartate hydrochloride were given orally per day. The placebo group received aspartic acid [1].

In the placebo group significantly more wome were hospitalized (80 vs. 48). Concerning the indications of admission to hospital, hemorrhage during pregnancy (17 vs. 4), incompetent cervix (17 vs. 8), and preterm labor (26 vs. 12) occurred more frequently in the placebo group. The median gestation was significantly longer in the women treated with magnesium (40 weeks vs. 39 weeks and 6 days); although the difference between the medians was not more than 1 day.

These results could be confirmed in another recently published study, in which 985 pregnant women were included. They got 15 mmol magnesium per day or placebo. In addition, these authors observed a reduction of the incidence of preeclampsia and eclampsia (5.6% vs. 3.7%) [17].

Serious interactions are not expected and no data have been published up to now. However, enteral iron absorption is described to be disturbed in the presence of magnesium. This might be due to gastric pH alterations, since magnesium salts are used as antacids. Preliminary data obtained with chloride-containing magnesium compounds (Mg-asp-HCl) show that in this combination no interactions occur.

2.2.2. *Effect on the Fetus*

The positive effect of magnesium supplementation seems to be longer gestational age. Admission of neonates to the intensive care unit was significantly less frequent than in the placebo group (36 vs. 20). In the subgroup of mothers regularly supplemented with magnesium, the incidence of babies below 2500 g could be reduced from 8.2 to 2.8%. They had significantly greater length (50 vs. 49) and head circumference, and fewer Apgar scores below 8 (0 vs. 5) [1].

In addition, a reduced incidence of intrauterine growth retardation by 10% could be demonstrated [17]. It would be worthwhile to study whether the development of newborn and small children is improved after a magnesium supplementation during pregnancy because offspring of rats supplemented with magnesium during pregnancy showed a better learning behavior than others exposed to a magnesium-deficient pregnancy [18].

2.3. High-Dose Magnesium Treatment

2.3.1. Eclampsia/Preeclampsia

In 1905 Meltzer and Auer [19] demonstrated a muscle-relaxing effect of intravenously applied $MgSO_4$. The first use of magnesium for the therapy of eclampsia was published by Riffmann in 1916 [20]. While in German-speaking countries this therapy did not at first gain acceptance, $MgSO_4$ became the routine therapy for eclampsia in the United States after the contributions of Lazard [21] and Dorsett [22].

It must be pointed out that this therapy makes use of pharmacological effects of high magnesium doses, blocking, for example, in a dose-dependent fashion the release of acetylcholine at the neuromuscular junction, or, generally speaking, of the calcium-antagonistic efficacy of magnesium.

Today two therapeutic procedures are carried out. In the case of an eclamptic seizure or a threatening seizure, a loading dose of 4 g $MgSO_4 \cdot 7H_2O$ (about 16 mmol magnesium) is slowly injected intravenously. Then a continuous infusion of 1 g $MgSO_4 \cdot 7H_2O$/hr (about 4 mmol/hr) is recommended [23]. The other schedule also starts with a loading dose of 16 mmol magnesium IV; then a second dose of 40 mmol is injected IM, followed by further injections of 20 mmol magnesium IM in alternate buttocks every 4 hr [24]. To reduce pain 1 ml of a 2% lidocaine solution may be added [25].

In numerous cases it could be shown that high-dosed $MgSO_4$ is a reliable therapy for eclampsia or preeclampsia with poor side effects; only in cases of extreme hypertension is combining with hydralacine recommended [25]. $MgSO_4$ has a high therapeutic range. It is necessary to know the side effects that occur with increasing serum magnesium concentrations: incidental reduction of blood pressure, nausea, vomiting, CNS depression, hyporeflexia, ECG changes, depression of respiration, coma, and finally cardiac arrest during a continuous increase of serum magnesium up to concentrations of 10 times the initial value [26]. It is worthwhile to pay attention to some drug interactions with magnesium [27].

During an effective therapy with parenteral magnesium, serum magnesium levels are usually found to range between 1.5 and 4.0 mmol/liter [28]. The effects on the fetus and newborn are discussed below.

2.3.2. *Preterm Labor*

Kumar and coworkers proved under in vitro and in vivo conditions that magnesium reduces the contractility of the human myometrium [29]. Magnesium exhibited better tocolytic effects than ethanol [30]. In cases of insufficient tocolytic effects, magnesium may be combined with infusions of β-adrenergic agents [31]. To reduce fetal respiration deficiency in case of delivery, lung maturation must be induced by glucocorticoids during tocolysis with β-adrenergic agents. During this procedure pulmonary edema is a rare but nevertheless known complication. The same complication may occur when magnesium is used [32].

3. OTHER ASPECTS

3.1. Calf Cramps

Actually, our first concern with magnesium came up when it proved effective against pregnancy-induced calf cramps. A woman suffering from preterm labor received oral magnesium supplements of 15 mmol because of calf cramps. To our surprise, not only did the cramps stop within a day but the clinical symptoms of preterm labor were also attenuated [15].

In a retrospective analysis it turned out that 6% of pregnant women suffer from calf cramps. In 19 of 21 women these cramps were alleviated after oral magnesium therapy (10 mmol/day) [33]. Since other drugs like quinine must not be prescribed to pregnant women, magnesium supplementation is actually a beneficial alternative in these cases.

3.2. Cardioprotection During Tocolysis

Magnesium deficiency significantly facilitates calcium influx into the cell. In fact, the application of catecholamines to magnesium-deficient laboratory animals caused extended necrosis of myocardial tissue. This effect is amplified by simultaneous medication with fluorocortisol. On the other hand, the development of necrosis was prevented by feeding diets highly enriched with magnesium as the

Mg-asp-HCl [34]. In light of numerous reports, pregnancy can be assumed to present a magnesium-deficient situation. During tocolysis with β-adrenergic agents an induction of fetal lung maturation by corticosteroids is often necessary. Therefore cardiotoxic effects of these substances may also result. Hence we proposed cardioprotection with magnesium in the form of 15 mmol Mg-asp-HCl/day in addition to β-adrenergic therapy [35].

4. MAGNESIUM IN THE NEWBORN

4.1. Physiological Aspects

A magnesium gradient across the placenta is assumed since fetal plasma magnesium levels are higher than maternal concentrations. This gradient, which is not due to differences in protein binding between mother and fetus [36], seems to be sufficient to protect the fetus against severe maternal magnesium deprivation. An active transport system from the mother to the fetus may explain the gradient but its existence has not yet been proven.

In rats experimental maternal magnesium deficiency showed profound adverse effects on reproduction. When severe magnesium deficiency existed during the whole gestation, 100% of the implantation sites of the fetus showed resorption. When magnesium-deficient diets where offered during the second half of gestation, about 20% of the offsprings showed a wide variety of malformations [37]. Under similar conditions of high neonatal mortality and pathological brain alterations of the newborns such as necrosis and reduction of tissue thickness could be shown [38]. Fetal anemia became obvious at a relatively mild magnesium deficiency, involving a reduction of hemoglobin and the erythrocyte count as well as macrocytosis associated with numerous microcytes and red cell fragments. A noticeable retardation was also observed when newborn rats were nursed by mothers receiving a magnesium-deficient diet. A period of magnesium deficiency of more than 3 months resulted in sterility of both males and females [39]. These experimental data indicate a need for the initiation of epidemiological studies.

4.2. Hypomagnesemia

In 1937 Nothmann described [40] fits in newborn babies and related them to hypomagnesemia. In a child of a mother with primary hyperparathyroidism, neonatal tetany was associated with hypomagnesemia [41]. When neonatal convulsions associated with hypocalcemia are not accompanied with hyperphosphatemia and when it is impossible to

normalize calcium concentrations unless the patient is treated with magnesium, hypomagnesemia may be the cause of the convulsions [42]. The origin of neonatal hypocalcemic tetany may be differentiated by two symptoms: hypomagnesemia and edema. Babies with a positive correlation between serum calcium and magnesium levels showing a rise of serum magnesium during calcium infusions had no pitting edema on the feet. On the other hand, babies with edema failed to show this phenomenon. Hence, secondary aldosteronism is suggested to be a contributory factor in the production of neonatal hypomagnesemia favoring the renal excretion of magnesium [43].

Another differentiation of neonatal tetany also seems possible: late onset of neonatal tetany occurs in primarily healthy babies, born at full term with normal birth weight mostly in winter or spring, and belonging to a lower socioeconomic class. They were usually fed cow's milk formula with a low calcium content and a low calcium-to-phosphorus ratio. Half of these patients exhibited hypomagnesemia and 60% had hyperphosphatemia [44]. Therefore, magnesium deficiency may play a central pathogenic role. In contrast to irritability as the main symptom of late neonatal tetany, early neonatal tetany is associated with hypotonia and reduced responsiveness occurring in the case of such perinatal disorders as prematurity, respiratory distress, and hyperbilirubinemia [44]. Here, except in prematurity, magnesium is scarcely involved.

It should be noted that (primary) hypomagnesemia can also be transferred genetically (see also Sect. 5.2). On the one hand, it is known that daughters of women with latent tetany also frequently suffer from this disease [45]. On the other hand, a case of primary hypomagnesemia with secondary hypocalcemia in a girl of consanguineous parents has been described in the literature and an autosomal recessive and X-linked inheritance is suggested [46]. Up to now approximately 30 similar cases have been described in the literature [11].

Other, less impressive symptoms than fits may be related to magnesium deficiency. Full-term newborn babies giving the clinical impression of hyperexcitability exhibited significant lower serum magnesium on the first day after delivery, and normalized at day 5 [47]. In studies on younger children polygraphic tracings showed relations between serum magnesium and the pattern of sleep. After magnesium injection "quiet sleep" increased and "active sleep" decreased [48].

Lower serum magnesium levels were found in infants who had been too small for their gestational age [49]. However, contradictory results are also reported [50].

4.3. Hypermagnesemia

Magnesium is easily transported through the placenta even against the gradient. Therefore, high serum magnesium concentrations are expected in the fetus following standard therapy of preeclampsia/eclampsia, when high quantities of magnesium are applied intravenously to the mother [51].

Hypermagnesemia in neonates was described [52] after $MgSO_4$ infusions to toxemic mothers. The serum magnesium levels of the umbilical cord reached levels up to 5.75 mmol/liter. The clinical manifestations in the newborn were similar to those in hypermagnesemic adults: lethargy, hypotonia, respiratory arrest, poor bowel movements, depressed reflexes. But it was also pointed out that the manifestation of acute or chronic intrauterine hypoxemia could account for some of these findings [52]. In severe cases only exchange transfusion may help to lower serum magnesium levels [53].

Pritchard's team, which has the most experience in the therapy of preeclampsia/eclampsia with magnesium sulfate, surveyed about 7000 infants whose mothers had received $MgSO_4$ parenterally. They administered 30—40 g $MgSO_4$/24 hr via intermittent intramuscular injections as long as maternal knee-jerk reflexes were demonstrable, when urine flow amounted to at least 100 ml/4 hr, and when respiration was not depressed. Up to now these authors have obtained no evidence that $MgSO_4$ administered prior to delivery to hypertensive mothers according to their schedule, effectively preventing eclamptic convulsions, was deleterious to their infants. Neonatal serum magnesium concentrations remained elevated during the first 72 hr of life (mean at 72 hr: 1.23 mmol/liter) [54]. In premature babies with birth asphyxia serum magnesium concentrations were found to be higher and may be associated with decreased muscle tone [55].

There are no apparent effects of maternal magnesium therapy on the neurological status of the neonate. Neurological performance of the neonate did not correlate with cord magnesium levels or with the total magnesium dose administered [55].

Fetal heart rate patterns are helpful in judging fetal oxygenation. The influence of $MgSO_4$ on fetal heart rate is discussed controversially. For example, a loss of variability of the fetal heart rate has been described [23,56], but other studies arrived at opposite results [57]. In an extended retrospective study [54] no negative effects on fetal heart rate pattern could be demonstrated during high-dose magnesium therapy of eclampsia/preeclampsia.

5. MAGNESIUM IN CHILDREN'S DISEASES

5.1. Physiological Aspects

5.1.1. *Normal Values*

In venous blood samples taken from the umbilical vein (n = 50) a concentration of 0.80 ± 0.18 (2 SD) mmol/liter was measured and 0.83 ± 0.18 (2 SD) mmol/liter in arterial blood serum using the AAS technique. These concentrations were significantly higher than the maternal levels of 0.71 ± 0.19 (2 SD) mmol/liter [58]. In children between 3 months and 14 years, magnesium levels of 0.99 ± 0.08 mmol/liter were measured. No statistical difference could be established between children of different ages [59]. Conversely, serum magnesium levels of newborns were significantly higher in the newborn (0.79 ± 0.008 mmol/liter) than in the mother (0.75 ± 0.008 mmol/liter). Newborns also exhibited higher serum calcium levels; since calcium is the direct regulator of PTH levels, it is not surprising that levels of the newborn were suppressed to undetectable traces [60].

5.1.2. *Magnesium Excretion*

In children between 1 month and 14 years, a renal magnesium excretion of 1.15 ± 0.45 mmol/kg per day (ranging between 0.37 and 2.14) was measured by AAS technique [61].

5.1.3. *Magnesium Requirements*

Fetal magnesium requirements were summarized by Seelig [11]. The requirement increases steadily up to term. Magnesium concentrations of diverse tissues increased with the weight gain of the fetus; therefore the fetal magnesium requirement becomes substantial in the last trimester of pregnancy.

As was already mentioned, nutritional changes of maternal food customs during pregnancy may occur but are still unproven. According to Karst and Möhr, most young women are consuming a magnesium-poor diet already before pregnancy [62].

On behalf of the newborn it is interesting to note that magnesium and calcium plasma levels are higher in breast-fed than in bottle-fed babies [63].

5.2. Primary Hypomagnesemia

The first clinical case of primary hypomagnesemia was described in 1965 by Paunier and coworkers [64]. Six cases of primary hypomagnesemia, all but one occurring in males, showed that the net intestinal absorption of magnesium was abnormally low due to its association with secondary hypocalcemia. No other laboratory evidence for malabsorption were detected and it was claimed that the mucosa was "normal" following microscopic evaluation. All patients developed severe tetanic convulsions which were corrected by magnesium infusions [65]. Interruption of magnesium supplementation led to a drastic fall of serum magnesium with an increase of three times the calcium magnesium ratio [66]. However, the intracellular calcium/magnesium ratio remained unchanged. For this purpose, samples of skeletal muscle were analyzed.

Three cases of primary hypomagnesemia showing typical clinical symptoms between days 19 and 35 of life have been described (one boy and two girls). They showed a greatly reduced intestinal absorption of ^{28}Mg in comparison to that of healthy adults. By a supplementation of 42—85 mmol Mg/day subnormal to normal serum magnesium levels were maintained [67].

5.3. Magnesium and Sudden Infant Death Syndrome

In 1969 Maresch speculated that changes in electrolytes are responsible for sudden infant death syndrome (SIDS) [68]. Later the hypothesis was advanced that "sudden unexpected death in infancy is a preventable condition resulting from the magnesium deprivation syndrome of growth" [69]. However, this hypothesis is not yet generally accepted [70].

On the other hand, a clear correlation has been established between the incidence of apnea and the supplementation of premature neonates with magnesium. Doses administered ranged between 0.2 and 0.5 mmol/kg per day [69].

5.4. Magnesium and Diabetes Mellitus

Tsang and his coworkers [71] first noticed characteristic alterations in infants of diabetic mothers. In contrast to babies of healthy mothers, these infants did not demonstrate increased plasma magnesium levels shortly after birth. These relatively decreased neonatal serum magnesium levels were correlated with the severity of maternal diabetes, to the mother's age, and to other clinical param-

eters. Interestingly, a negative correlation between serum magnesium levels and the duration of maternal diabetes was shown [72].

In the case of children developing diabetes mellitus, it is well known that serum magnesium levels are significantly lower than that of nondiabetic controls [73]. The degree of hypomagnesemia correlates with glycolysated hemoglobin, but not with glucosuria. Nevertheless, an increased urinary loss of magnesium is probably the main reason for the developing magnesium deficit.

5.5. Neurological, Psychiatric, and Vegetative Disturbances

Magnesium is also correlated with neurology and psychiatry. Significantly lowered magnesium levels were found [74] in depressive and in schizophrenic children. On the other hand, positive effects of magnesium in combination with vitamin B_6 on autistic children could be shown. In these patients not only behavioral improvement but also significant modifications of both biochemical and physiological parameters were demonstrated [75]. The diagnosis of spasmophilia is apparently quite difficult to establish. It is advisable to look for specific symptoms in the "nervous" child [76]. The disease may present somatic or psychic features. In some cases pain is located in the abdomen; in other cases the major symptoms are difficult to separate from neurosis. No correlation was found between clinical symptoms and biochemical data. The criteria for the final diagnosis was the efficacy of magnesium therapy [77]. In the same context, case reports on bruxism may be interpreted as describing a reduction of symptoms after magnesium supplementation [78].

Similar to latent tetany known in female adults [79], a disturbance of breathing regulation can occur in children; improvement by high-dose oral magnesium medication is described in the literature [80].

5.6. Magnesium in Other Diseases

Severe diarrhea is frequently associated with hypomagnesemia and, subsequently, with tetanic spasm [81]. Regardless of the specific cause, frequent watery stools seem to be an important cause of magnesium depletion [82].

Hypomagnesemia is also described in children with cirrhosis. This is related to a secondary hyperaldosteronism because of a reduced degradation of aldosterone which is known to increase renal magnesium excretion [83,84].

In juvenile chronic arthritis serum magnesium levels differ significantly in phases of highest and smallest inflammatory activity [85].

Hypomagnesemia was found in one-forth of children with urolithiasis [86]. These data were not confirmed by other authors [87]. The fact that, opposite to adults, children with renal failure are showing hypomagnesemia is not understood [88].

An important decrease of magnesium in muscle biopsy specimens of patients suffering from Duchenne dystrophy implicates magnesium along with calcium as another pathophysiological factor in this disease [89].

6. CONCLUSION

The efficacy of high-dose parenteral magnesium administration in preeclampsia and eclampsia is well documentated and generally accepted. It makes use of pharmacological, mostly calcium-antagonistic effects of magnesium.

Adverse metabolic effects of a pregnancy-induced magnesium deficit have been noticed by obstetricians only in recent years, resulting in multiple disturbances of mothers, the fetuses, and newborns. Appropriate magnesium supplementation during pregnancy has meanwhile been shown to improve maternal health as well as the course of pregnancy and fetal outcome.

Magnesium deficiency seems to negatively influence metabolic homeostasis, resulting in multiple disturbances. That may be the reason for the impressive effect of magnesium supplementation in pregnancy.

Magnesium deficiency is also the primary factor in numerous diseases of newborns and children. CNS alterations may be most obvious. Psychovegetative disturbances are difficult to prove scientifically. The diseases are as diverse as the role of magnesium in metabolism and may be caused by "microlesions of metabolism".

A diversified nutrition with nonpurified products, e.g., whole-meal bread, may avoid disturbances of magnesium homeostasis in healthy persons. Situations of greater need, such as pregnancy, should be supplemented and recognized magnesium deficiency should be treated with magnesium.

Well-designed studies are necessary to better characterize magnesium-deficient situations, so that physicians can become more conscious of the role of magnesium in man.

ABBREVIATIONS

AAS	atomic absorption spectrophotometry
CNS	central nervous system
IV	intravenous
$MgSO_4$	magnesium sulfate
Mg-asp-HCl	magnesium-aspartate-hydrochloride
PTH	parathyroid hormone
SIDS	sudden infant death syndrome
SD	standard deviation

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