

Original Research

## Analysis of serum Calcium, Magnesium, and Parathyroid Hormone in neonates delivered following preeclampsia treatment

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**Abstract:** Due to the approximate clinical and biochemical manifestations of calcium and magnesium disturbances, with regard to the regulatory effects of parathyroid hormone (PTH), this present study is designed to analyze serum calcium (Ca), magnesium (Mg), and (PTH) at the time of birth, 24 hours afterwards in newborns after the mother has been treated with Mg-sulfate. We registered 86 term and preterm neonates (43 in each group) using simple census method delivered through vagina to preeclampsia pregnant women treated with Mg-sulfate immediately before birth in Khorramabad Asali Hospital, Iran. The first specimen was obtained from umbilical cord blood at birth, followed by the second sample of 2cc peripherally obtained from blood 24 hours after birth. The mean serum Mg level was higher than normal for both specimens in both term and preterm groups with no significant difference. The mean serum Ca level was higher in term group at both occasions, which turned out to be statistically significant ( $P < 0.000$ ) and ( $P = 0.001$ ) for the first and second specimens respectively. The mean PTH level was also in normal range for both groups at both times with no statistical significance. On the other hand, magnesium level showed a significant decline at 24 hours ( $P = 0.005$ ) while PTH increased significantly ( $p < 0.000$ ) and ( $p = 0.005$ ) for term and preterm groups respectively. In contrast, Ca changes were not significantly different between the two specimens. Treatment with Mg-sulfate immediately before vaginal delivery increases Mg in both term and preterm neonates with no effect on Ca and PTH levels.

**Key words:** Preeclampsia, neonatal hypermagnesemia, PTH, magnesium sulfate.

### Introduction

Past decade has been distinguished by few advances with respect to the pathophysiology and prevention (1), but several modifications has been made in preeclampsia patient's clinical treatment (2). Particularly, approval have been contrived for home or day-care management of a chosen group of patients with moderate gestational hypertension or preeclampsia (3). Three randomized clinical trials showed that anticipated management with close monitoring of maternal and fetal conditions is attainable in a selected group of patients with serious preeclampsia at less than 34 weeks' gestation (4).

Moreover, the efficacy of  $MgSO_4$  in the control and prevention of eclamptic convulsion has been confirmed in randomized controlled trials carried out worldwide (5). In comparison, recent randomized trials was aborted to show any major potency from the habitual use of low-dose aspirin in pregnancy (6), whereas a recent meta-analysis found calcium supplementation amid pregnancy to be useful in cutting down the risk of hypertension (7).

Preeclampsia is defined as a specific pregnancy syndrome that can affect every organ with occurrence of gestational hypertension, proteinuria exceeding 300 mg in 24 hours, headache, and visual disturbances (8). It may lead to eclampsia with generalized convulsions, before, during or after labor. The best agreed treatment for both preeclampsia and convulsions is the administration of  $MgSO_4$  (9, 10). Drug toxicity presents as weakness of deep tendon reflexes, respiratory and urinary output changes, that are more reliable markers relative to total serum or ionized Mg measurements (11).

Magnesium passes through placenta and fetal membranes and its modulation has parallel changes in the mother's blood (12). The Mg distribution volume reaches a plateau approximately 3-4 hours after administration (10). Although it is considered safe to both mother and the newborn, but, it causes neonatal hypermagnesemia and hypocalcaemia in adult (13).

Despite wide recognition of Ca as a PTH regulator, Mg also contributes to the feedback mechanism of PTH / Ca / P regulation as its reduction causes PTH reduction, which in-turn reduces Ca (14). The dosage and the duration of treatment with Mg-sulfate alters the mother and newborn Mg and Ca levels (15).

The symptoms of neonatal hypermagnesemia include respiratory depression, failure to pass meconium, hyporeflexia, lethargy, and flaccidity (16). This, in conjunction with the resulting poor feeding, causes a myriad of differential diagnosis, the most famous being neonatal sepsis (17). The empirical steps to treat neonatal sepsis precede the measures taken to either prove or rule it out, and sometimes appear cumbersome and unnecessary, with devastating adverse effects (18).

This together with lack of significant information about the prevalence and indications of Mg, Ca, and PTH changes in newborns following Mg-sulfate treat-

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ment, made us design the present study in order to analyze the Mg, Ca, and PTH levels in both the term and preterm offspring of preeclampsia mothers following Mg-sulfate treatment (19).

**Materials and Methods**

Following approval from the Ethics Committee of the University Research Center for our descriptive study, we registered 86 pregnant women presented with the diagnosis of preeclampsia as a simple continuous sample. The preeclampsia defined as either systolic blood pressure of 140mmHg or more or diastolic blood pressure of 90mmHg or more, or both, in addition to at least one symptom of edema or proteinuria (defined as 300mg protein in a 24-hour urine collection or 20mg in a spot sample).

All mothers are provided with full explanation about the procedures, they consented to participate in accordance to informed consent codes. The neonates were divided into two groups each containing 43 newborns, namely, preterm and term groups. The preterm newborn were delivered 20 and 37 weeks during the gestation period, and the term newborn were delivered after 38 weeks. It is worth to mention that we excluded any birth other than the natural vaginal delivery.

We integrated the routine protocol of our center for administration of Mg-sulfate as a primary 15g injection, of which 10g was delivered intramuscularly, and 5g intravenously. This is followed by 5g intramuscularly every 6 hours as the maintenance dose. If the mother had taken more than three doses in addition to the primary dose, she would have been excluded from the study, as the same as a mother who would need caesarian section considering obstetrics indications. The intravenous injection was provided by 5% dextrose water solution.

The exclusion criteria were as follows: (1) neonatal mortality, (2) newborns whose mothers were presented with pain and gave birth to a baby before taking Mg-sulfate, (3) any co-morbidity, (4) any other drug taken before or during labor, (5) caesarian section, and (6) lack of informed consent for participation.

The first specimen were obtained immediately after birth as 2cc cord blood by the attending labor staff. The second specimen acquired 24 hours after birth by an expert technician from a peripheral vessel. The laboratory measurements of PTH were performed using Radioimmunoassay technique (RIA) and that of Ca and Mg was done by photometry.

All data were collected via a checklist integrating information about age of mother, age of pregnancy, blood pressure at presentation, the history of chronic hypertension, the frequency of Mg-sulfate administration, apgar score of the first and fifth minutes postpartum, the sex of the newborn, and the lab results.

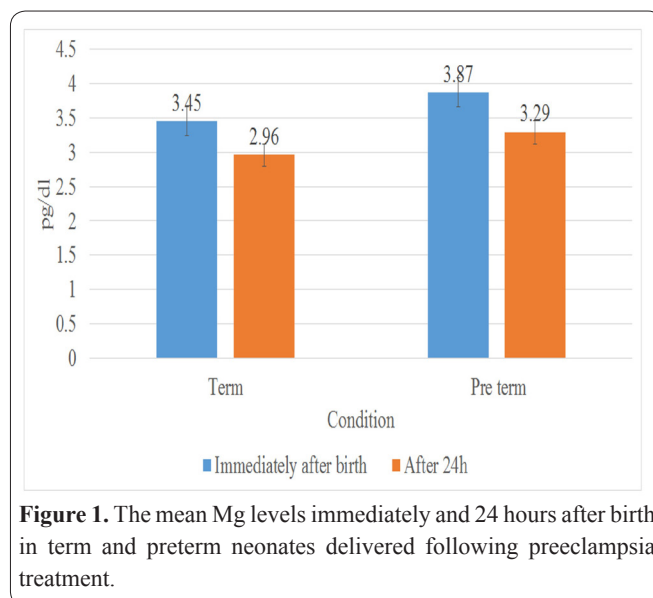
All the relevant data analyzed by SPSS software and the parameters were compared between preterm and term groups. We used t-test, chi-square, and fisher test to analyze correlations, and mean±SD for descriptive purposes.

**Results**

We finally acquired 86 participants after screening some. The mean age of mothers was 25.94 ± 5.28 (17-38y) years and the mean gestational age was 38.11 ± 7.82 (31-40w) weeks. The mean systolic and diastolic blood pressures at presentation were 156.15 ± 12.5 (140-210mmHg) and 98.65 ± 10.29 (80-130mmHg), respectively. Thirty-eight percent (38%) of the offspring were female and the remaining were male. The apgar scores at 1 minute was seven or higher in 70 (81.4%), five to seven in 10 (11.6%), and three to five only in 6 (7%) preterm neonates. The apgar scores at 5 minute were seven or higher in 79 (91.8%), five to seven in 7 (8.2%) and none of the newborns had he score under 5.

Baby first day in life, 58.7 percent of the preterm and 47.6 percent of the term group had hypermagnesemia. Figure 1 show the mean Mg levels immediately and 24 hours after birth. Hypermagnesemia was detected in 65.11 percent of the total population at birth and 40.69 percent after 24 hours (table1). This difference of measurements immediately after birth and at 24 hours afterwards, was significant neither for the term nor for the preterm group (p = 0.216 and p = 0.22, respectively).

The fisher test proved a significant reduction in Mg levels at 24 hours after birth in comparison to the first specimen in both term and preterm groups (P = 0.05). None had levels below normal range. While 29 preterm and 27 term neonates had hypermagnesemia at birth, 21 preterm and 14 term neonates still had increased levels



**Figure 1.** The mean Mg levels immediately and 24 hours after birth in term and preterm neonates delivered following preeclampsia treatment.

**Table 1.** Serum Ca, Mg, PTH levels in the study population immediately after birth and 24 hours after that.

Biochemical parameters	Term		Preterm	
	at birth	24 hours after birth	at birth	24 hours after birth
Mg (mg / dl)	3.45 ± 1.09	2.96 ± 0.87	3.87 ± 1.35	3.29 ± 1.03
Ca (mg / dl)	9.58 ± 0.9	9.41 ± 0.93	8.84 ± 0.8	8.71 ± 0.97
PTH (pg / dl)	16.29 ± 13.08	28.85 ± 5.37	12.42 ± 13.21	24.29 ± 17.27

<sup>1</sup> The normal ranges according to the reference lab; PTH: 6.2-29pg / dl; Ca: 8.5-11 mg / dl; Mg: 1.8-3 mg / dl.

at 24 hours. There was no significant difference between these two groups ( $P = 0.39$ ).

The mean Ca level in term and preterm neonates at birth and 24 hours after birth have been shown in figure 2. The t-test showed significant correlation for both groups either at birth or 24 hours after birth ( $p = 0.003$  at birth and  $p = 0.001$  24 hours after birth). In other words, although Ca levels were normal in both term and preterm groups, it was significantly higher in term neonates at both occasions (table1).

We also found hypocalcaemia at birth to be 46.5 and 11.6 percent of the preterm and term offspring respectively. Interestingly, hypercalcemia was detected in 9.3 percent of term infants which was not the case in preterm neonates. There was no significant correlation between first and second specimens in term ( $p = 0.372$ ) and preterm ( $p = 0.249$ ) groups.

The mean PTH level in term and preterm groups at birth and 24 hours later have been presented in figure3. Twenty four (55%) preterm and 34 (79%) term infants at birth, and 22 (51%) preterm and 32 (74%) term infants at 24 hours after birth had normal PTH levels (table1).

The t-test showed no significant difference between groups at either first or second occasions ( $P = 0.42$  at

birth and  $P = 0.44$  at 24 hours). However, the fisher test proved the significance of the increase in PTH levels at 24 hours in both groups ( $P < 0.000$  for term and  $P = 0.005$  for preterm group). The chi-square test was insignificant for both groups at both timings ( $P = 0.25$  and  $P = 0.21$ , respectively).

## Discussion

Parenteral magnesium sulfate therapy is routinely utilized for capturing prophylaxis in preeclampsia management. Magnesium is crucial constituent of calcium homeostasis, along with calcitonin, vitamin D, parathyroid hormone, and phosphorus (20). Even though the impact of magnesium sulfate infusion on the levels of different serum constituents have been addressed, the comprehension of maternal homeostasis is left incomplete because the levels of vitamin D have not been measured. Reports on the effects of maternal therapy on neonatal and fetal calcium homeostasis are incomplete and in-accurate, and effects on the vitamin D constituents have not been previously recorded (21).

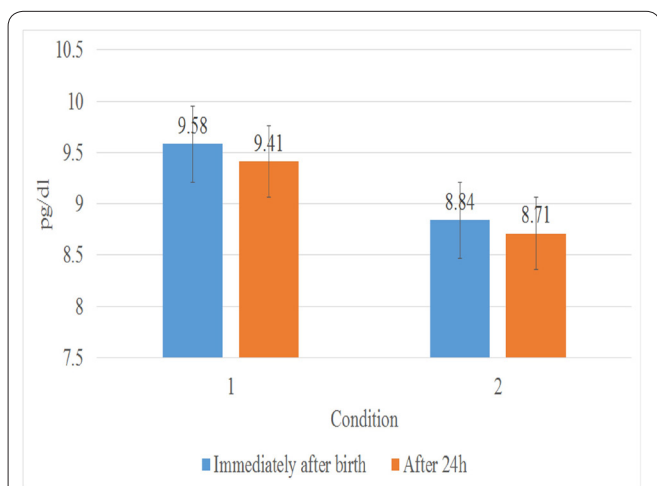
As we have described fully in our result, both the term and preterm groups had hypermagnesemia after birth. Although the Mg level declined in both groups 24 hours after birth, which was significant in comparison to the first-hour specimen, there was no significant correlation between the two groups (22). The Ca and PTH were normal at both occasions in both groups.

Green et.al (1983) (23) in their study found hypermagnesemia with normal Ca in the offspring of Mg-sulfate treated mothers. They also described neurologic status of the newborns and concluded no difference in comparison to control group and no correlation with cord Mg or the total Mg administered (24). This is important as hypermagnesemia may affect neurologic status of the newborn adversely, thus resulting in diagnostic confusion (25). We limited our study to neonates and avoided measurements in mothers as a matter of technical and financial difficulties, but our results are closely comparative to Green's study.

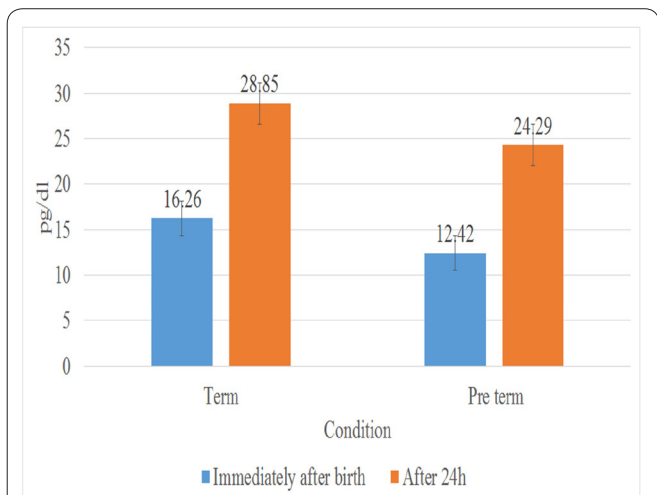
Rantonen et al., 2001 studied (15) the effects of maternal magnesium sulphate treatment on the parathyroid hormone secretory response and mineral status of neonates studied, 8 participants were exposed to MgSO<sub>4</sub> and 27 control preterm infants amid the first 2 week of life (26). Hypermagnesemia resulted during the first 3–7 days of life without influencing the concentrations of other serum constituents. They concluded that hypermagnesemia was related with hypercalciuria at the first 3 days and PTH suppression up to the age of 2 weeks in the exposed infants (27).

To evaluate the therapeutic effects of Mg-sulfate on mineral and PTH response, Rantonen et.al (2001) found hypermagnesemia and hypercalcemia in the first week of life with PTH suppression (28). This was in contrast to our findings which showed hypercalcaemia in only a minimal of term cases. We did not detect either hypercalcemia or PTH suppression. This was the case in Van Der Hayden et.al research, who, in contrast to our study, also detected elevated potassium and calcium in cord blood immediately after birth (29).

McGumrus et.al (1980) (30) designed a case-control study on 37 neonates born to mothers treated with Mg-



**Figure 2.** The Mean Ca levels immediately and 24 hours after birth in term and preterm neonates delivered following preeclampsia treatment.



**Figure 3.** The mean PTH levels immediately and 24 hours after birth in term and preterm neonates delivered following preeclampsia treatment.



sulfate for preeclampsia using serial measurements and found hypermagnesemia immediately, and at hours 2, 12, and 24 after birth. This reached a comparable level of controls after 48 hours. Calcium levels were normal.

Donovan *et al.* (1980) (31) considered Ca, Mg, and PTH changes in 20 preeclampsia patients treated with Mg-sulfate, and detected hypermagnesemia in the first 72 hours concomitant with hypercalcemia and reduced PTH levels. They concluded that hypermagnesemia causes calcium shift from bone to plasma. This is important because Matsuda *et al.* also described hypermagnesemia as a cause for transverse bands in the metaphysis of long bones which is indicative of bone mineral loss (32).

As the Schanler *et al.* (1997) (32) have shown, premature neonates born to prolonged Mg-sulfate treated mothers had increased Mg, phosphorus, osteocalcin levels with concomitant hypocalcemia. We cannot comment on these findings because we did not use prolonged treatment in our study.

Calcium supplementation at the time of pregnancy decreases maternal mean arterial pressure (33) and the prevalence of preeclampsia, yet, the molecular basis is not well understood. These findings are generally supportive of our findings. The differences in results relating to Ca and PTH level may be caused by the difference in frequency or duration of Mg-sulfate administration. However, it should be emphasized that Ca is not the only factor affecting PTH level and Mg levels are also relevant (34).

In a study by August *et al.*, a reduction in the levels of  $1\alpha$ , 25-dihydroxycalciferol and parathyroid hormone levels was reported not to be significantly different from controls group in nine subjects with acute preeclampsia before magnesium sulfate therapy. These findings seem to be different from ours.

Preeclampsia is associated with abnormal calcium metabolism and placental dysfunction. Yusuf (2012) (35) investigated ionized calcium levels in the umbilical cord arterial blood of women with preeclampsia and normotensive pregnancies. There was no difference in the cord pH and fetal growth restriction between the two groups. Ionized calcium levels were significantly lower in the preeclampsia group ( $p < 0.001$ ).

Although some studies showed significant changes in serum trace elements levels like Ca and Mg in preeclampsia and eclampsia, but we do not examine these elements before starting magnesium sulfate treatment. It can influence the exchange of circulation of Mg and Ca between mothers and neonate.

In term neonates, Mg sulfate exposure may be associated independently with NICU admission in a dose-dependent relationship. Requirements for fluid and nutritional support are common in this group, likely due to feeding difficulties in exposed neonates. Assessment of acute care needs among all neonates exposed to Mg sulfate for maternal eclampsia prophylaxis should be considered. These increasing risk for NICU admission may be as a result of serum Mg level changes in neonates that we showed in our study (36).

Although maternal and neonatal magnesium concentrations were highly correlated [but we did not examine the serum Mg level in mother and neonate simulta-

neously, which limited our study.

It is noteworthy that we faced some limitations during the study, which might have influenced or results. First, the time schedule was limited and we encountered many mothers' did not consent when selecting our participant. This caused reduction of the total cases. Second, we had to limit our study design to cases with no controls, which would certainly reduce the accuracy of our conclusions. There were also technical obstacles such as inability to obtain second specimens, or the delay in analysis because of occupied laboratory timetable.

If the administration of Mg-sulfate is inevitable to prevent preeclampsia adverse effects, the hypermagnesemia should be considered as an important contribution in the case of hyporeflexia, hypotonia, or coma in the newborn. In totality, we should conclude that administration of Mg-sulfate in order to prevent preeclampsia adverse effects causes hypermagnesemia in both term and preterm neonates with no effect on Ca and PTH levels. Our results also emphasize the need for further studies on the calcium status of infants born to mothers with preeclampsia.

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