Original Research Article

The study of association between maternal serum magnesium levels and preterm labour in a tertiary care hospital

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ABSTRACT

Background: Serum magnesium level in pregnancy is a valuable tool to find out preterm onset of labour. In the asymptomatic group, greater surveillance and administration of steroids, tocolytics and transfer to a higher centre wherever necessary has to be done with mothers with low serum magnesium level. The objective of the study is to find association between serum magnesium levels and women with preterm labour, and to compare these values with those patients who have a term delivery.

Methods: The subjects included 100 pregnant women with preterm labour (cases) between 28 and 37 weeks gestation (Group A) and similar number of pregnant women with term labour (controls) between 37 and 40 weeks (Group B). Inclusion criteria for cases was singleton pregnancy, painful uterine contractions more than two in 30 minutes, intact fetal membranes, cervical dilatation (at least 1 cm) and effacement (80%). Serum magnesium levels were done in both the groups. Patients were followed until delivery. Routine antenatal investigations were done. Serum levels of magnesium were estimated by Erba's semi auto-analyser.

Results: 62% patients in Group A were from rural areas. More patients in Group A (70%) were from low socioeconomic class. More women in Group A were anaemic (44%). Mean value of hemoglobin in Group A was 9.93gm/dL. More patients in Group A had muscle cramps (89%). VLBW (<1500gm) neonates were more in Group A (21%). Also, LBW (1500-2499gm) neonates were more in Group A (60%). Mean neonatal birth weight in Group A (1907.3gm) was less. Neonatal morbidity and mortality was observed significantly more in Group A. Mean serum magnesium was less in Group A. Mean serum magnesium levels in primi and multigravida patients were less in Group A. Moreover, mean serum magnesium levels were less in urban and rural patients in Group A. Mean serum magnesium levels were less in normal and overweight patients in Group A. Also, mean serum magnesium levels were less in patients with cervical dilatation <3cm and >3cm in Group A.

Conclusions: Low maternal serum magnesium level is associated with preterm labour. Patients with preterm labour have significantly low serum magnesium level when compared with labour at term.

Keywords: Maternal serum magnesium, Preterm labour, Term delivery

INTRODUCTION

Preterm labour is occurrence of regular uterine contractions and cervical changes in a woman with intact fetal membranes and gestational age <37 weeks.[1] Uterine contractions without cervical change is also a marker of threatened preterm labour.[2] Magnesium is the second important positively charged ion found within the cells of body. It acts as a cofactor in more than 300 enzyme reactions. It activates those enzymes and plays an

important role in the nerve conduction and contractile response of smooth muscles. Pregnancy is marked by a state of relative hypomagnesaemia and varied hypomagnesaemia is observed in preterm labour. Hypomagnesaemia leads to neuromuscular hyper-excitability resulting in muscle cramps and uterine hyper-activity.[3]

Magnesium plays an important role in pregnancy for the formation of new tissues, both maternal and fetal. Pregnant women require higher magnesium intake than the normal non-pregnant women of same age. Normal serum levels of magnesium in third trimester of pregnancy range from 1.1 to 2.2 mg/dL.[2]

Magnesium deficiency results in fatigue, confusion, irritability, weakness and hypertension, loss of appetite, insomnia, nausea, vomiting, diarrhoea, defect in nerve conduction and muscle contraction. Its deficiency during pregnancy is also associated with preterm labour, pre-eclampsia, small for gestational age (IUGR) foetus, leg cramps as well as sudden infant death syndrome.[4]

Estimation of serum magnesium levels in pregnancy may prove to be a valuable tool in the prediction of preterm onset of labour. This can help to provide greater antenatal surveillance in the asymptomatic group, and administration of steroids, tocolytics and transfer to a higher centre in those with symptoms of preterm labour.[5] This study was conducted in a tertiary care hospital of north India to find association between serum magnesium levels and women with preterm labour, and to compare these values with those patients who had a term delivery.

METHODS

This observational case-control study was conducted for a period of one year in the Postgraduate Department of Obstetrics and Gynaecology, SMGS Hospital, Government Medical College, Jammu after due approval from Institutional Ethics Committee. The subjects included 100 pregnant women with preterm labour (cases) between 28 and 37 weeks gestation (Group A) and similar number of pregnant women with term labour (controls) between 37 and 40 weeks (Group B). Inclusion criteria for cases was singleton pregnancy, painful uterine contractions more than two in 30 minutes, intact fetal membranes, cervical dilatation (at least 1 cm) and effacement (80%). Pregnant women with fibroid uterus, cervical incompetence/any uterine malformation, previous history of recurrent abortions/preterm delivery, with multiple pregnancy, ruptured membranes, placenta previa, known or detected fetal abnormality, polyhydramnios and significant medical/surgical history were excluded from the study. Controls were selected on the same day as that of cases by simple random sampling. Informed consent was taken from all the subjects.

All the patients were subjected to thorough history taking including socio-economic status, systemic and obstetric examination. Laboratory investigations were done as per hospital protocol. Serum magnesium levels were done in both the groups. Patients were followed until delivery. Routine antenatal investigations were done. In patients with preterm labour, following additional investigations were done in addition to the routine: USG for fetal well being and cervical length, CRP. Maternal outcome included mode of delivery. Fetal outcomes included IUGR, AFD, birth weight, MAS and any neonatal complications like jaundice/respiratory distress /neonatal death/ IVH were noted. Serum levels of magnesium were estimated by Erba's semi auto-analyser.

Statistical analysis

All data collected was analyzed using computer software Microsoft Excel and SPSS version 21.0 for Windows. Data was reported as mean±standard deviation and proportions as deemed appropriate for quantitative and qualitative variables respectively. The statistical difference in mean value between two groups was tested using unpaired 't' test. The qualitative data was compared using Fisher's exact test/Chi-square test. ANOVA (analysis of variance) was also performed to evaluate statistical significance in more than two groups. A p-value of <0.05 was taken as significant. All p-values reported were two-tailed.

RESULTS

In both, Group A (cases) and Group B (controls), majority of patients were in the age group of 21 to 30 years (83% and 85% respectively), with mean age being comparable in both the groups (24.96 versus 25.04 years, p=0.88). Parity-wise, 74% and 78% patients were primigravida in Group A and Group B respectively. Statistically, the difference being non-significant (p=0.50). Mean gestational age in Group A was 33.69 years, while in Group B it was 37.97 years. Mean body mass index in both the groups was comparable (23.55 versus 23.85kg/m², p=0.17) with majority of patients having normal BMI in both the groups (81% and 76% respectively).

According to place of residence, 62% patients in Group A and 27% patients in Group B were from rural areas, the difference being statistically significant (p<0.0001). Majority of patients in both the groups were housewives (85% and 90%), difference being statistically not significant (p=0.39). More patients in Group A (70%) were from low socioeconomic class as compared to Group B (55%), difference being statistically significant (p=0.04). More women in Group A were anaemic (44%) as compared to Group B (37%). Mean value of hemoglobin in Group A was 9.93gm/dL and in Group B was 10.19gm/dL, the difference being statistically significant (p=0.03). Similarly, more patients in Group A had muscle cramps (89%) as compared to Group B (51%), the difference being statistically significant (p<0.0001). Cervical dilatation in both the groups was

comparable (75% versus 70%, p=0.34). Similarly, vaginal delivery in both the groups was comparable (92% versus 93%, p=0.78). VLBW (<1500gm) neonates were significantly (p=0.004) more in Group A (21%) as compared to Group B (5%). Also, LBW (1500-2499gm)

neonates were significantly (p<0.0001) more in Group A (60%) as compared to Group B (11%). Mean neonatal birth weight in Group A (1907.3gm) was significantly (p<0.0001) less as compared to that of Group B (2723.6gm).

Table 1: Neonatal morbidity and mortality in Group A and Group B.

Neonatal Morbidity/Mortality	Group A (n=100) No. (%)	Group B (n=100) No. (%)	Statistical interpretation (Chi-square test)
Respiratory distress syndrome (RDS)	33 (33.00)	2 (2.00)	χ^2=31.16; p<0.0001*
Intraventicular haemorrhage (IVH)	11 (11.00)	–	–
Meconium	20 (20.00)	4 (4.00)	χ^2=10.65; p=0.001*
Jaundice	49 (49.00)	4 (4.00)	χ^2=49.69; p<0.0001*
Intrauterine growth retardation (IUGR)	11 (11.00)	2 (2.00)	χ^2=5.26; p=0.02*
Still birth	1 (1.00)	–	–
Death	8 (8.00)	–	–

*Highly significant

Table 2: Group comparison for serum magnesium levels.

Serum magnesium level (mg/dL)	Group A (n=100) No. (%)	Group B (n=100) No. (%)	Statistical interpretation (Chi-square test)
<1.1	66 (66.00)	23 (23.00)	χ^2=35.56; p<0.0001*
1.1-1.79	21 (21.00)	29 (29.00)	χ^2=2.28; p=0.13**
≥1.80	13 (13.00)	48 (48.00)	χ^2=23.72; p<0.0001*
Total	100	100	-
Mean ± Standard deviation (Range) (mg/dL)	1.10±0.40 (0.7-2.1)	1.58±0.46 (0.7-2.2)	-
Statistical interpretation (Unpaired t test)	t=7.38; p<0.0001; Highly significant		

*Highly significant; **Not significant

Table 3: Relationship of age with mean serum magnesium level.

Age group (in years)	Serum magnesium level				Statistical interpretation (Unpaired t test)
	Group A		Group B		
	No.	Mean±SD (mg/dL)	No.	Mean±SD (mg/dL)	
≤20	9	1.32±0.42	7	1.3±0.47	t=0.96; p=0.35**
21-25	47	1.13±0.41	56	1.62±0.43	t=5.52; p<0.0001*
26-30	36	1.03±0.40	29	1.51±0.50	t=3.89; p=0.0002*
≥31	8	1.01±0.30	8	1.74±0.49	t=3.59; p=0.002*

*Highly significant; **Not significant

Table 4: Relationship of parity with mean serum magnesium level.

Parity	Serum magnesium level				Statistical interpretation (Unpaired t test)
	Group A		Group B		
	No.	Mean±SD (mg/dL)	No.	Mean±SD (mg/dL)	
Primigravida	74	1.18±0.41	78	1.65±0.43	t=6.88; p<0.0001*
Gravida 2 and 3	26	0.88±0.29	22	1.32±0.46	t=4.02; p=0.0002*

*Highly significant

Neonatal morbidity and mortality was observed significantly more in Group A as compared to Group B

(Table 1). Mean serum magnesium was significantly (p<0.0001) less in Group A (1.10mg/dL) as compared to

Group B (1.58mg/dL) (Table 2). Mean serum magnesium levels in the age groups of 21-25, 26-30 and >31 years were significantly less in Group A as compared to those of Group B (Table 3). Similarly, mean serum magnesium levels in primi and multigravida patients were significantly less in Group A as compared to those of Group B patients (Table 4). Moreover, mean serum magnesium levels were significantly less in urban and rural patients in Group A as compared to those of Group B (Table 5). Similarly, mean serum magnesium levels were significantly less in normal and overweight patients in Group A as compared to those of Group B (Table 6). Also, mean serum magnesium levels were significantly less in patients with cervical dilatation <3cm and >3cm in Group A as compared to those of Group B (Table 7).

Table 5: Relationship of place of residence with mean serum magnesium level.

Place of residence	Serum magnesium level				Statistical interpretation (Unpaired t test)
	Group A		Group B		
	No.	Mean±SD (mg/dL)	No.	Mean±SD (mg/dL)	
Urban	38	1.31±0.41	73	1.68±0.42	t=4.43; p<0.0001[*]
Rural	62	0.97±0.35	27	1.30±0.44	t=3.77; p=0.0003[*]

*Highly significant

Table 6: Relationship of body mass index with mean serum magnesium level.

BMI (kg/m^2)	Serum magnesium level				Statistical interpretation (Unpaired t test)
	Group A		Group B		
	No.	Mean±SD (mg/dL)	No.	Mean±SD (mg/dL)	
18.5-24.9 (Normal weight)	81	1.10±0.40	76	1.57±0.47	t=6.76; p<0.0001[*]
25-29.9 (Overweight)	19	1.11±0.43	24	1.59±0.41	t=3.73; p=0.0006[*]

*Highly significant

Table 7: Relationship of cervical dilatation with mean serum magnesium level.

Cervical dilatation	Serum magnesium level				Statistical interpretation (Unpaired t test)
	Group A		Group B		
	No.	Mean±SD (mg/dL)	No.	Mean±SD (mg/dL)	
<3 cm	75	1.19±0.40	70	1.72±0.37	t=8.26; p<0.0001[*]
≥3 cm	25	0.83±0.28	30	1.24±0.47	t=3.82; p=0.0003[*]

*Highly significant

In Group A, mean value of serum magnesium among gestational age groups 28-30, 31-33 and 34-37weeks was found to be 1.13, 1.11 and 1.08mg/dL respectively, the difference however was not significant (p=0.90).

DISCUSSION

Magnesium deficiency in pregnancy is likely to cause perinatal complications which may last throughout life. In the present study, mean serum magnesium level was 1.10±0.44mg/dL in patients with preterm labour while it was 1.58±0.46mg/dL in patients with term labour, the difference being statistically significant. Sixty-six percent patients with preterm labour had low serum magnesium level (<1.1mg/dL). This finding showed that preterm labour was associated with low serum magnesium level. Preterm birth is the single major cause associated with neonatal morbidity and mortality in both developing and developed world.

This result is in accordance with the study of Shahid et al. in which significantly more patients with preterm labour (60%) had serum magnesium level <1.9mg/dL.[6] Bhat et al, found that patients in preterm labour group had a significantly depressed mean serum magnesium level as compared to normal pregnancy (1.34 mEq/L vs. 1.87 mEq/L; p<0.001).[7] Mahmoud et al, found that patients with preterm labour had significantly reduced serum magnesium level (mean 1.55mg/dL versus 1.81mg/dL) for those who delivered at term (p<0.032).[8] Jenabi et al, also found positive association between maternal serum magnesium levels and preterm labour.[9]

The mean maternal age in our study (24.96 years for preterm group and 25.04 years for term group) was consistent with the studies of Mahmoud et al, (24.31 versus 26.52 years) and Jenabi et al, (24.56 vs. 25.18 years).[8,9] However, it was lower in preterm group as compared to study conducted by Bhat et al, (28.63 years).[7] The difference can be explained due to early age

of marriage and lesser use of contraceptives methods in our study.

In the present study, 74% patients in preterm labour group were primigravida, which is in accordance with the study of Khani et al. (75%).[10] Mean gestational period in our study was 33.69 weeks in preterm labour group and 37.97 weeks in term group, the difference being statistically significant (p<0.0001). Similarly, Begum and Das found mean gestational age of 33.03weeks and 38.95 weeks in patients with preterm and term labour.[5]

In our study 62% patients with preterm labour and 27% patients with term labour were from rural areas, the difference being statistically significant (p<0.0001). The difference was due to high rate of referrals of preterm pregnancies to our hospital (tertiary health care centre) from peripheral rural areas where NICU facilities were not available. Similarly, Kumar also found 65% of patients with preterm labour were from rural areas.[11]

Also, in our study 85% patients with preterm labour were house wives. The increase in preterm labour among housewives could be due to poor prenatal care. This result is in accordance with the studies of Mahmoud et al, and Khani et al, who also reported that 85% and 90% patients with preterm labour were housewives.[8,10]

In the present study, 70%, 22% and 8% patients with preterm labour and 55%, 32% and 13% with term labour belonged to low, middle and high socioeconomic class respectively, the difference being statistically significant (p=0.04). Bhat et al, found patients with preterm labour belonging to low socioeconomic class were significantly higher than the middle and higher socioeconomic classes (58% in preterm labour patients and 45% in term, p<0.05).[7] Mahmoud et al, also found that in preterm labour group lower socioeconomic class was significantly higher than the middle and upper socioeconomic classes.[8] Patients belonging to low socioeconomic classes have stressful lifestyle, inaccessible medical care and diet deficient in micronutrients including magnesium.

In our study 44% patients with preterm labour and 37% patients with term labour were anaemic. Mean value of haemoglobin came out to be 9.93 gm/dL and 10.19 gm/dL respectively in patients with preterm and term labour. The difference was statistically significant (p=0.03). These results were in accordance with the study of Manzoor et al, who found mean haemoglobin of 9.13±1.54gm/dL in 48.6% of patients with preterm labour.[12]

83% patients with preterm labour and 51% with term labour in our study reported the incidence of muscle cramps. The difference was statistically highly significant (p<0.0001). Our findings were similar to the observations of Bhat et al, Mahmoud et al, and Shaikh et al, who reported percentage of patients with preterm labour having history of muscle cramps as 89%, 73% and 46.7%

respectively.[7-9] Neuromuscular hyperexcitability is an initial problem cited in individuals who have magnesium deficiency resulting in muscle cramps and uterine hyperactivity leading to premature onset of labour.[13]

In our study low birth weight neonates were significantly more in patients with preterm labour with percentage of 60% and 11% in patients with term labour. Mean neonate birth weight in preterm neonates (1907.3gm) was significantly less (p<0.0001) than term neonates (2723.6 gm). 33% and 49% neonates of patients with preterm labour got admitted to NICU due to RDS and jaundice. IUGR was present in 11% neonates in patients with preterm labour. Neonatal morbidities like IVH (11%), still birth (1%) and neonatal mortalities (8%) were observed in neonates of patients with preterm labour only. Similarly, Khani et al, reported that low birth weight neonates were 80% in patients with preterm labour.[10] In a study conducted by Shaikh et al, IUGR was significantly higher 41.3% patients with preterm labour (p<0.001).[13] Almonte et al, found that reduced free magnesium concentration in both maternal and offspring blood and an increased incidence of periventricular hemorrhage.[15]

Magnesium deficiency in pregnancy is likely to cause perinatal complications which may last throughout life. 66% of patients in our study with preterm labour had low serum magnesium level (<1.1mg/dL). This finding shows that preterm labour was associated with low serum magnesium level. Mean serum magnesium level in our study came out to be 1.10±0.44mg/dL in patients with preterm labour while it was 1.58±0.46mg/dL in patients with term labour. Difference was statistically significant with p<0.0001. This result is in accordance with the study of Shahid et al, where significantly more patients (60%) with preterm labour had serum magnesium level <1.9 mg/dL.[6] Jenabi et al, also found positive association between maternal serum magnesium levels and preterm labour.[9]

In our study mean serum magnesium level was found to be less in all age groups among patients with preterm labour as compared to patients with term labour. However, in age groups 21-25 years, 26-30 years and >31 years the difference was highly significant (p<0.0001 and p=0.0002 and p=0.002 respectively). While in age groups <20 years the difference was not significant (p=0.35). It was observed in our study that high maternal age was associated was low serum magnesium levels in the preterm labour group. This is likely a result of higher demands of pregnancy at an age characteristic of poor nutrition. This is similar to the study of Sharma et al., who found that serum magnesium levels decreased with advanced maternal age.[16] However, in a study by Begum and Das, serum magnesium level was independent of maternal age.[5] This variation in result may be due to less number of patients taken in their study groups.

In our present study mean serum magnesium level in primigravida with preterm labour and term labour was found to be 1.18±0.41mg/dL and 1.65±0.43mg/dL. Multigravida had levels of 0.88±0.29mg/dL and 1.32±0.46mg/dL in the preterm and term labour group. The difference was statistically significant in both with p<0.0001 and p=0.0002. It was observed that multigravida had low magnesium levels as compared to primigravida in both the groups. Kumar correlated serum magnesium levels among pregnant women with increasing parity and found that pregnant women with parity 2 and more had lower serum magnesium level when compared to primigravid. He found that in primiparous pregnant women, mean serum magnesium value was 1.77±0.34mg/dL. Serum magnesium level in pregnant women with 2nd and 3rd parity was 1.58±0.19 and 1.52±0.26mg/dL respectively.[11] Pathak et al, also found a significant decrease (p=0.01) in serum magnesium with the increase in parity. Pregnant women with parity 2 or more had a significantly lower serum magnesium level (1.77±0.35mg/dL) compared to nulliparous pregnant women (2.01±0.57mg/dL).[17]

In our study mean serum magnesium level was found to be significantly less in patients residing in rural (0.97±0.35mg/dL) as well as urban (1.31±0.41mg/dL) areas with preterm labour as compared to patients with term labour (1.30±0.44 and 1.68±0.42mg/dL; p=0.0003 and <0.0001 respectively). However, Kumar and Sharma et al, in two different studies reported that serum magnesium levels showed slight decrease in both rural and urban pregnant women cases compared to controls but the difference was statistically not significant.[11,16]

In our study mean serum magnesium level was found significantly higher in women who were overweight than normal weight patients in both preterm and term labour patients (p<0.0001 and 0.0006 respectively). This was in accordance with the study of Begum and Das, who found that in both the groups, mean serum magnesium level was higher in women with BMI >25kg/m^2 compared to BMI ≤25kg/m^2.[5]

Mean level of magnesium was found to be 1.69±0.21mg/dL and 2.08±0.21mg/dL in patients with BMI >25kg/m^2 and 1.62±0.17mg/dL and 1.95±0.16mg/dL in patients with BMI ≤25kg/m^2 in preterm and term patients in the present study. The result was also statistically significant with p<0.001. Mean serum magnesium level was obsereved to be 1.19±0.40 and 1.72±0.37mg/dL in patients with cervical dilatation <3 cm in preterm and term labour group respectively. Patients with cervical dilatation >3 cm mean level was found to be 0.83±0.28 and 1.24±0.47mg/dL in preterm and term labour group respectively. The difference was statistically significant. The hyperexcitabilty of uterine musculature due to hypomagnesemia leads to cervical changes resulting in preterm delivery. In our study mean value of serum magnesium was <1.1mg/dL in 34-37 weeks gestational age group. Mean levels of serum magnesium among gestational age groups 28-30, 31-33 and 34-37 weeks was found to be 1.13±0.20, 1.11±0.39 and 1.08±0.44mg/dL respectively. Bhat et al. found mean serum magnesium level of 1.37±0.055, 1.35±0.065 and 1.31±0.060mg/dL respectively in preterm gestational age groups 28-30 weeks, 31-33 weeks and 34-36 weeks with lowest levels at 34-36 weeks period of gestation.[7] Mahmoud et al, found that in 28-30 weeks gestational age group level was 1.843±0.70mg/dL, 31-33 weeks 1.309±0.369mg/dL and 34-36 weeks 1.23±0.28mg/dL.[8] With these studies it was found that magnesium level decreases with increasing gestational which may be due to physiological hemodilution in pregnancy contributing to the onset of preterm labour.

Decrease in magnesium plays an important role in physiology of parturition. Hypomagnesemia causes inhibition of adenyl cyclase with resultant increase in cytoplasmic calcium levels. Calcium by its action on calmodulin activation brings about uterine contraction, while magnesium prevents uterine contractions. Magnesium level may affect the blood flow through the uterus and may contribute towards lysosome stabilization. Hypomagnesemia, therefore, may be either a causative factor or simply reflect the process involved with the devepolment of uterine irritability in preterm labour.

CONCLUSION

In this study, low maternal serum magnesium level was associated with preterm labour. Patients with preterm labour had significantly low serum magnesium level when compared with labour at term. This study recommends that important steps should be taken to prevent and treat magnesium deficiency as it has direct implication on mother as well as fetus.

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