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Original Research Article

Serum magnesium level at 24 to less than 37 weeks: a prospective cohort study predicting spontaneous preterm delivery

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ABSTRACT

Background: Preterm labour is a leading cause of perinatal morbidity and mortality. Out of various causes, many macronutrients and micronutrients are said to have a role in pathogenesis of preterm labour, one of them is magnesium. Magnesium inhibits myometrial contractions by antagonizing calcium mediated uterine contractions. With advancement of pregnancy serum magnesium levels falls causing hyper excitability of neuromuscular junction bringing in uterine hyperactivity. The study was aimed to measure and compare the level of serum magnesium in preterm labour and normal pregnancy and to find the association of serum magnesium level with preterm labour.
Methods: This cohort observational study was done in Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow and eligible participants i.e., pregnant women with singleton gestation between 24 and <37 weeks of gestation were enrolled.112 women with preterm labour and 120 with no preterm labour were taken as study and control group respectively, serum magnesium level measured and followed till delivery.
Results: The study showed mean serum magnesium level was 1.79±0.22 mg/dl in study group as compare to 1.98±0.25 mg/dl in control group and the difference was statistically significant ($p<0.001$). The value of Serum Magnesium below 1.885 mg/dl had a sensitivity of 64.8% and specificity of 66.1%.
Conclusions: We can conclude that low serum magnesium is associated with preterm labour and serum magnesium estimation in pregnancy may be a valuable marker of predicting preterm labour.

Key words: Serum magnesium level, Preterm labour, Perinatal morbidity and mortality

INTRODUCTION

The journey of a preterm baby is often one step forward and two steps backwards. Prematurity has become a significant obstetric concern in recent years. Preterm birth is a leading cause of neonatal morbidity and mortality.[1,2] Moreover, its long term sequelae pose a serious problem for the offspring and mother.[3] One out of every eight babies is now born prematurely.[4] According to WHO (Feb 2018), the rate of preterm birth ranges from 5% to 18% worldwide.[5] In developing countries (like India) the rate of preterm birth on average is 12%, whereas in developed countries it is 9%.[5] Preterm labour is labour which occurs with regular and frequent uterine contractions causing progressive cervical changes before 37weeks of gestation while preterm birth is delivery of a viable pregnancy at <37weeks of gestation.[5]

A fetus is nurtured in the womb and protected from outside world, but for various reasons when gestation is shortened preterm labour tries to expel this in the world. The preterm labour is a multifactorial condition; 50% being spontaneous. The remaining 50% of preterm labours are probably the result of prelabour rupture of membrane (PROM), infection, multiple gestations, polyhydramnios, cervical incompetence, antepartum hemorrhage and

possible socio-economic, geographical and nutritional factors.[6-8]

Despite of varied etiology, preterm labour may be due to an alteration in basic biochemical functions of the body at cellular level. For biochemical processes in cell, it is important to maintain electrolyte status. Out of various electrolytes Magnesium is a subject of interest nowadays.[9] Magnesium acts as a physiological antagonist of calcium. Magnesium inhibits myometrial contractions by antagonizing calcium mediated uterine contractions. High concentrations of extracellular magnesium prevent calcium entrance into myometrial cells by inhibiting calcium channels.[10] It is known that with advancement of pregnancy serum magnesium levels falls which plays an important role in the physiology of parturition.[11] So it can be hypothesized that decrease of magnesium in plasma may be responsible for initiation of uterine contractions and preterm labour. Hence this study was aimed to look for serum magnesium level in women with preterm labour and normal pregnancy which may be valuable in predicting preterm labour.

METHODS

This cohort observational study was done in department of obstetrics and gynecology in collaboration with Department of Pathology, King George Medical University, Lucknow over a period of one year. Women between 24 weeks to <37 weeks of pregnancy with labour pains or without labour pains attending antenatal clinic and those admitted in Department of Obstetrics and Gynaecology, Lucknow were enrolled after excluding prelabour rupture of membranes (PROM), previous history of preterm delivery, polyhydramnios, antepartum hemorrhage, multiple pregnancy, cervical incompetence, uterine anomalies, any maternal or fetal complications needing early termination.

All enrolled women between 24 weeks to <37 weeks pregnancy were subjected to detailed history of present pregnancy, past history, obstetric history, family history, socioeconomic history, nutritional history. Thereafter, general physical examination, systemic examination, per abdominal examination, per speculum examination and per vaginal examination if indicated were carried out. All routine antenatal investigation (if not done earlier) and various investigations relevant with the case were carried out along with serum magnesium measurement. The estimation of serum magnesium was done by Calmagite EGTA - Colorimetric method. Thereafter all enrolled women were followed till delivery. 242 women were enrolled in the study and were divided into study group (112) and control group (120). Women who came with preterm labour pains, tocolysis given(if indicated) and then patients followed till delivery. Women with no preterm labour pain were 130. They were followed till delivery. Out of 130, 120 delivered at term. 7 women lost to follow up so they were excluded from study. 3 patients had preterm delivery. Since preterm delivery number was very less so they were excluded from study. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software.

RESULTS

We enrolled 232 pregnant females, out of these 112 (48.3%) developed pre-term labour pain were classified as Study group and rest 120 (51.7%) who didn't develop preterm labour pain were classified as Control group. The demographic profile of enrolled women in both groups were noted and illustrated in Table 1. No difference in respect to maternal age, religion, dietary habits, gestational age at the time of serum magnesium estimation was observed between the two groups. Proportion of pregnant women of lower socioeconomic status were significantly higher in study group (20.5%) as compare to control group (8.3%). Mean BMI of pregnant women enrolled in study group (19.95±2.02 kg/m^2) was significantly low as compared to that of control group (21.22±2.71 kg/m^2). Proportion of underweight (BMI <18.5 kg/m^2) women was higher in study group as compared to control group. Mean serum magnesium in study group was 1.79±0.22 mg/dl and in control group it was 1.98±0.25 mg/dl and the difference was statistically significant (p<0.001) (Table 2).

Mean serum magnesium level estimation was done at various gestational age as illustrated in (Table 3). Females of Control group had higher levels of Serum Magnesium levels as compared to Study Group irrespective of gestational age of estimation i.e., 24-28 weeks (2.00±0.22 vs. 1.78±0.28 mg/dl), 28+ to 32 weeks (1.99±0.22 mg/dl vs. 1.64±0.23 mg/dl) and 32+ to <37 weeks (1.97±0.26 vs. 1.82±0.21 mg/dl). Difference in S. magnesium between two groups was not found to be significant at gestational age 24-28 weeks but it was significant at gestational age 28 weeks 1 day to 32 weeks and 32 weeks 1 day < 37 weeks.

The serum magnesium level was noted in respect to demographic profile of enrolled women in both groups and illustrated in (Table 4). In both the groups serum magnesium was found to be almost similar in all age groups but control group had significantly higher serum magnesium levels as compared to study group in all the age groups. Control group had significantly higher serum magnesium levels as compared to study group for both Hindus and Muslims. Women with lower socioeconomic status in both study group and control group had lower serum magnesium level as compared to middle and upper socioeconomic status women. Control group had higher S. magnesium levels as compared to study group in all the socio-economic class, but significant differences were observed only in Middle Socio-economic class.

Non- vegetarian women in both study group and control group had higher serum magnesium levels as compared to vegetarian women but the difference was not significant.

Table 1: Distribution of groups according to demographic profile.

Variable	Study Group (N=112)		Control Group (N=120)		Total	
	Frequency	%	Frequency	%	Frequency	%
Age (years)						
Mean age±SD (Range)	25.84±4.27 (18-38)		26.47±4.19 (19-40)		26.16±4.23 (18-40)	
t=1.129; p=0.260						
Religion						
Hindu	94	83.9	101	84.2	195	84.1
Muslim	18	16.1	19	15.8	37	15.9
χ^2=0.002 (df=1); p=0.961						
Socio-economic status						
Lower	23	20.5	10	8.3	33	14.2
Middle	87	77.7	104	86.7	191	82.3
Upper	2	1.8	6	5.0	8	3.4
χ^2=8.368(df=2); p=0.015						
Dietary habits						
Nonveg	18	16.1	19	15.8	37	15.9
Veg	94	83.9	101	84.2	195	84.1
χ^2=0.002 (df=1); p=0.961						
Nutritional Status (BMI kg/m^2)						
Mean BMI±SD (Range) kg/m^2	19.95±2.02 (16.1-26.0)		21.22±02.71 (17.2-30.2)		20.61±2.48 (16.1-30.2)	
t=3.989; p<0.001						
Gestational age at the time of Estimation of serum Magnesium						
24-28 weeks	5	4.5	11	9.2	16	6.9
28 weeks, 1 day- 32 weeks	16	14.3	26	21.7	42	18.1
32 weeks, 1 day - <37weeks	91	81.3	83	69.2	174	75.0
χ^2=4.729 (df=2); p=0.094						

Table 2: Level of serum magnesium (mg/dl) in different groups.

Group	N	Serum magnesium levels (mg/dl)			
		Min.	Max.	Mean	SD
Study Group	112	1.12	2.35	1.79	0.22
Control Group	120	1.16	2.57	1.98	0.25
Total	232	1.12	2.57	1.89	0.25

In both study group and control group, there was significant subsequent increment of serum magnesium levels with the BMI. Underweight (BMI <18.5 kg/m^2) had low serum magnesium levels as compared to normal (BMI 18.5-24.9 kg/m^2) and overweight (BMI 25-29.9 kg/m^2). Control group had higher S. magnesium levels as compared to study group in all the nutritional states, difference was significant only in Normal nutritional status.

The (Figure 1) shows area under curve on Receiver-operator curve (ROC) of Magnesium levels for prediction of preterm labour pain and it was 0.722 with 95% confidence interval, ranging from 0.658 to 0.787, indicating a projected accuracy of prediction to be 72.2%.

Based on the direction of assessment, Serum Mg level for prediction of pre-term labour pain at a cut-off with a smaller value indicating positive prediction. On exploring the cut-off value, serum magnesium <1.885 mg/dl was found to be 64.8% sensitive and 66.1% specific. Calculated positive predictive value and negative predictive value at this cut-off were 63.4% and 65.8% respectively in our study.

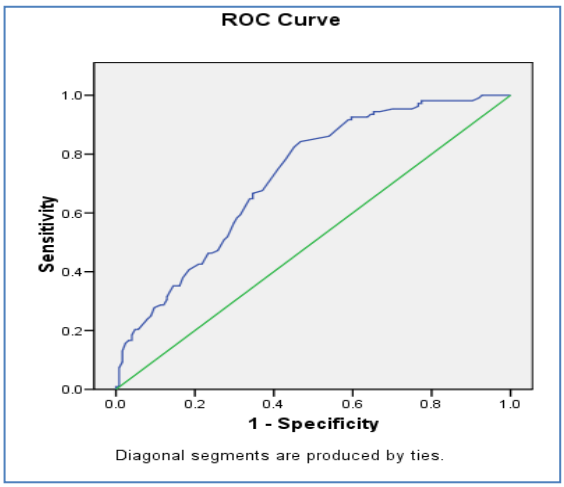

Figure 1: ROC curve.

Table 3: Comparison of magnesium levels at different gestational age (within group and between group comparison).

GA at estimation of Mg levels	Study Group (N=112)			Control Group (N=120)			Between Group comparison		Overall (N=232)		
	N	Mean	SD	N	Mean	SD	T value	P value	N	Mean	SD
24-28 wks	5	1.78	0.28	11	2.00	0.22	1.711	0.109	16	1.93	0.26
28 wks 1 d to 32 wks	16	1.64	0.23	26	1.99	0.22	4.941	<0.001	42	1.86	0.28
32 wks 1 d to <37 wks	91	1.82	0.21	83	1.97	0.26	4.192	<0.001	174	1.89	0.25
Within Group Comparison	F=4.896 (ANOVA); p=0.009			F=0.121 (ANOVA); p=0.886			-		F=0.562 (ANOVA); p=0.571		

Table 4: Association of serum magnesium with demographic profile in both the groups.

Variable	Study Group (n=112)		Control Group (n=120)		Total	
	N	Mean±SD (S. Magnesium)	N	Mean±SD (S. Magnesium)	T value	P value
Age (years)						
18-25	61	1.79±0.21	56	1.92±0.26	-3.028	0.003
26-30	36	1.79±0.19	45	2.04±0.23	-5.032	<0.001
>30	15	1.79±0.34	19	2.00±0.23	-2.095	0.044
Within group comparison	F=0.002 (ANOVA); p=0.998 NS		F=3.041 (ANOVA); p=0.052 NS			
Religion						
Hindu	94	1.79±0.22	101	1.97±0.25	-5.318	<0.001
Muslim	18	1.78±0.25	19	1.99±0.24	-2.652	0.012
Within group comparison	t=0.174; p=0.862 (NS)		t=0.364; p=0.717 (NS)			
Socio-economic status						
Lower	23	1.72±0.21	10	1.85±0.30	-1.357	0.184
Middle	87	1.81±0.23	104	1.99±0.24	-5.268	<0.001
Upper	2	1.79±0.07	6	1.97±0.25	-0.978	0.366
Within group comparison	F=1.403 (ANOVA); p=0.250		F=1.512 (ANOVA); p=0.225			
Dietary habits						
Nonveg	18	1.80±0.26	19	2.02±0.27	-2.541	0.016
Veg	94	1.79±0.22	101	1.97±0.25	-5.372	<0.001
Within group comparison	t=0.114; p=0.910 (NS)		t=0.757; p=0.451 (NS)			
Nutritional status (BMI kg/m^2)						
Underwt.	24	1.71±0.22	14	1.79±0.31	-0.932	0.358
Normal	84	1.80±0.21	95	1.99±0.22	-5.613	<0.001
Overweight	4	2.07±0.23	9	2.15±0.24	-0.554	0.591
Obese	0		2	2.07±0.38	–	–
Within group comparison	F=5.277 (ANOVA); p=0.006		F=4.725 (ANOVA); p=0.004			

DISCUSSION

In the present study, majority of women in both study group and control group were in the age group 18-25years (54.5% & 46.7% respectively) followed by 26-30years (32.1% & 37.5%), rest >30 years (13.4% & 15.8%). The mean maternal age in study group and control group was 25.84±4.27 and 26.47±4.19 yrs respectively. Similar findings were suggested by Begum et al.[12] They found that 50 % cases with preterm labour were of <25years age and it was not significantly different from control group (42.5%). In present study 20.5%, 77.7% and 1.8 % study group and 8.3%, 86.7% and 5.0% in control group belong to lower, middle and upper socioeconomic class respectively and the difference was statistically significant (p=0.015).

Table 5: ROC characterization parameters.

Area under curve	Standard Error	P value	95% CI	
			Lower bound	Upper bound
0.722	0.33	<0.001	0.658	0.787
Cut-off value of serum magnesium	**Sensitivity**	**Specificity**	**PPV**	**NPV**
<1.885 mg/dl	64.8%	66.1%	63.4%	65.8%

Similar findings were suggested by Nedra Whitehead who concluded that preterm deliveries were 50% more common in lower income group and 40% more common in women who had <12years of education.[13] The increase in preterm labour in low socioeconomic class may be due to poor prenatal care, stressful life style and nutritional deficiency of trace elements including magnesium. In our study, we found that serum magnesium was low in lower socioeconomic class as compare to middle and upper class in both study group (1.72±0.21 mg/dl vs. 1.81±0.23 mg/dl vs. 1.79±0.07 mg/dl) and control group (1.85±0.30 mg/dl vs. 1.99±0.24 mg/dl vs. 1.97±0.25 mg/dl). Similar results were seen in study done by AA Begam et al who showed no significant difference in serum magnesium level between low and middle income groups in study group (1.61±0.17 mg/dl vs. 1.67±0.19 mg/dl; p>0.1) while in control group, there was significant difference (1.92±0.13 mg/dl vs. 2.06±0.21 mg/dl; p<0.01).[12]

Sharma et al also observed highly significant fall in serum magnesium levels in women belonging to low and middle socioeconomic strata as compared to those in high socioeconomic group in both the groups (Study group1.23±0.08 mg/dl vs. 1.51±0.16 mg/dl vs. 1.84±0.14) (Control group 2.00±0.17 mg/dl vs. 2.57±0.35 mg/dl vs. 3.0±0.17 mg/dl) (p<0.001) thus relating the low level of magnesium with lower class. Mean BMI of pregnant women in study group (19.95±2.02) was found to be significantly lower as compared to control group (21.22±2.71). Our results are similar to the study done by AI Girsen et al and Salihu et al where they concluded that there is increased risk of preterm delivery in women of underweight BMI categories at pre-pregnancy.[14-16] It was seen that with increasing BMI, serum magnesium level increased and in overweight group in both study and control group it was significantly higher as compare to normal BMI group. Similar results were seen in a study done by Begam et al.[12] A healthy diet plan and interventions to reduce pre-pregnancy underweight can be a valuable strategy to reduce preterm birth.

In our study, we found that in study group (women with preterm labour) mean serum magnesium was 1.79±0.22 mg/dl and in control group (women with no preterm labour) mean serum magnesium was 1.98±0.25 mg/dl and the difference was statistically significant (p<0.001). The findings were consistent with the results of the studies of Uludag et al which concluded that serum magnesium was significantly lower in preterm labour patients (1.6 mg/dl) as compare to controls (1.8 mg/dl).[17]

Mahmoud et al also found that serum magnesium was significantly (p<0.032) reduced in preterm delivered group (1.552±0.658 mg/dl) in compare to those delivered at term (1.81 ± 0.735 mg/dl). These findings are similar to the results of Lotfalizadeh et al who analysed the significant difference between serum magnesium level in women with preterm labour and normal pregnancy (1.80±0.17 mg/dl vs. 1.97±0.19 mg/dl, p=0.04).[18,19] Therefore, the lower serum magnesium level reflected the tendency of preterm labour or initiation of preterm labour. In our study we found that serum magnesium declined with advancement of gestation. Similar results were suggested by Arikan et al who analysed the continuous decline of serum magnesium from 19 weeks of gestation to term and the greatest decline was from 19 weeks to 28 weeks gestation. This state of hypomagnesaemia can be due to either increased demand or increased excretion in pregnancy.[20-22]

Prophylactic oral magnesium supplementation to the women at higher risk of preterm labour may be beneficial for prevention of preterm births and perinatal morbidity and mortality. Kawagoe et al in their multi-institutional intention to treat trial concluded that magnesium sulphate is better as an adjuvant tocolytic rather than as a replacement. Zarean et al showed the preventive effect of oral magnesium (200 mg efferevescent Mg tablet from Vitafit company once a day) in lowering preterm birth (p=0.044).[23,24] Thus it can be seen that magnesium is an effective tocolytic agent and of comparable value with existing tocolytic agents.

Our study had shown a sensitivity of 64.8%, specificity of 66.1%, positive predictive value 63.4%, negative predictive value 65.8% and diagnostic accuracy 72.2% for serum magnesium below 1.885 mg/dl in prediction of preterm labour. The findings in our study demonstrated that serum magnesium concentration is decreased in preterm labour. Therefore, serum magnesium estimation in pregnancy may be a valuable marker of predicting preterm labour.

Limitations

Limitations of the study were relatively small study cohort and 50% cases of preterm labour are idiopathic; so all idiopathic cases could not be ruled out in our study.

CONCLUSION

After doing a comprehensive analysis of all the above observations, the final conclusion that can be drawn from

the present study is that women with preterm labour had low level of serum magnesium as compared to women with no preterm labour. Because of its association, it can be used as a biomarker for prediction of preterm labour. Although many predictive tests are available for preterm labour having poor sensitivity and specificities and are very expensive, serum magnesium measurement is a cost-effective test amounting no economical burden on the women. Early identification of at-risk women can potentially decrease the prevalence of preterm birth and reduce the economic & emotional burden on the families and women in terms of care of premature infants. Women with magnesium deficiency can have nutritional counselling. The diet with rich source of magnesium can be advised to women at risk. Moreover, magnesium supplements in the form of tablets and capsules can be prescribed to women at higher risk of preterm delivery. We propose that further studies are required to establish the role of Serum Magnesium as a predictor of Preterm Labour.

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