

Serum Magnesium Levels as a Predictive Marker for Preterm Labour: A Prospective Case–Control StudyVeladanda Kavitha¹, Arjumand Bano², Mandala Madhumitha³¹Assistant Professor, Department of Gynaecology & Obstetrics, Chalmeda Anand of Medical Sciences, Karimnagar, Telangana, India²Assistant professor, Department of Gynaecology & Obstetrics, Chalmeda Anand of Medical Sciences, Karimnagar, Telangana, India³Post-Graduate (3rd Year), Department of Gynaecology & Obstetrics, Chalmeda Anand of Medical Sciences, Karimnagar, Telangana, India

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Abstract:**Background:** Preterm labour, or the onset of labour at <37 completed weeks of gestation, is a leading cause of neonatal morbidity and mortality globally. Early recognition of women at risk is important for early intervention. Magnesium is important to neuromuscular stability and uterine quiescence and hypomagnesemia has been implicated in the pathophysiology of preterm labour. Estimation of serum magnesium levels may be a useful and inexpensive predictive method for antenatal care.**Objectives:** To assess the serum levels of magnesium in women with preterm labour and to compare these levels with the level in women delivering at term, and to assess the utility of serum magnesium as a predictive marker for preterm labour.**Materials and Methods:** This prospective case control study was carried out in a tertiary care hospital and admitted 200 pregnant women; 100 women in the preterm labour group (28-36 weeks of gestation) and 100 women in the term pregnancy group (37-40 weeks). Detailed clinical evaluation was done and socioeconomic status was determined by Modified Kuppaswamy scale. Serum magnesium levels were estimated by colorimetric Calmagite technique. Statistical analysis was done by using Students t test and Chi square test with $p < 0.05$ as significant.**Results:** The mean serum level of Mg was significantly decreased in preterm labour as compared to term group (1.49 ± 0.09 mg/dL vs 2.06 ± 0.11 mg/dL; $p < 0.001$). Hypomagnesemia (<1.8 mg/dL) was noted in 61.0% of the women who had preterm labour compared to 29.5% of the women who had delivered in term ($p < 0.001$). Serum magnesium levels were not significantly related to the maternal age, parity or the socioeconomic. In female studies, those with lower serum levels of magnesium had higher levels of uterine activity and shorter delivery time.**Conclusion:** A low level of maternal serum magnesium has a significant link to preterm labour. Serum magnesium estimation is an easy-to-perform, inexpensive and clinically useful tool that can potentially help in the identification of women at an increased risk for preterm labour to allow for closer surveillance and early intervention.**Keywords:** Preterm labour, Hypomagnesemia, Colorimetric Calmagite Technique.**DOI:** 10.25258/ijcpr.18.6.175This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Preterm labour, the onset of labour before 37 completed weeks of gestational age, is one of the significant obstetric challenges worldwide, and is a major cause of neonatal morbidity and mortality worldwide [1]. Despite improvements in antenatal care, the rate of preterm birth remains high, especially in low- and middle-income countries, and accounts for a significant proportion of poor neonatal outcomes including respiratory distress syndrome, low birth weight, sepsis and long-term

neurodevelopmental impairment. [2] Early identification of women at risk for preterm labour is therefore very important to allow timely implementation of preventive and therapeutic interventions.

The causes behind preterm labour are multifactorial and involves infection, inflammation, overdistension in uterus, cervical insufficiency, hormonal imbalance and biochemical changes [3].

Among biochemical factors, more and more attention has been paid to the role played by trace elements, especially magnesium, because of its physiological role in neuromuscular transmission and smooth muscle relaxation [4]. Magnesium is a natural calcium antagonist, and is important for maintaining the quiescence of the uterus during pregnancy by attributing to inhibition of the myometrial contractility [5].

Several studies have shown that there is a significant association between low serum magnesium levels in mothers and preterm labour. Meena and Maheshwari found significantly lower serum levels of magnesium in women having pre-term labour than in those delivering at term [6] and hence its potential as a predictive biomarker. Similar results were found in observational and comparative studies from varied populations, and these consistently demonstrated lower serum levels of magnesium in women presenting with a problem of preterm labour [7-9]. Ferdous et al. and Mahboobunnisa et al. further alluded to the link between hypomagnesemia and heightened labour complications and adverse perinatal outcomes [10,11].

Prospective and predictive studies have investigated the diagnostic value of serum estimation of magnesium in antenatal women. A prospective cohort study of serum magnesium concentrations between 24 and <37 weeks of gestation showed moderate sensitivity and specificity for predicting spontaneous preterm delivery at defined cut-off values for magnesium concentrations [12]. Advanced analytical approaches, such as predictive modelling, have also demonstrated that serum magnesium concentrations may be used for improved risk stratification for preterm labour, in addition to clinical parameters [13].

Systematic reviews and meta-analyses have further supported the link between low magnesium status and risk of preterm birth, highlighting the possible value of serum magnesium evaluation as an easy, inexpensive screening tool in routine antenatal care [14]. However, despite accumulating evidence, still no consensus has emerged on optimal cut-off values and its standalone predictive accuracy. This study attempts to evaluate the serum magnesium levels as an indicator for preterm labour and to further establish the clinical relevance of the same in identifying the high-risk pregnancies.

Materials and Method

This study was conducted as a prospective case control study carried out in the Department of Obstetrics and Gynaecology in the tertiary care teaching hospital over a defined study period after receiving approval of the Institutional Ethics Committee. Written informed consent was obtained from all subjects before they were enrolled. The

study population comprised women who were pregnant and aged 18-45 years and with singleton pregnancies. A total of 200 participants were included, and 100 were split into each of two groups consisting of women.

The study group consisted of 100 pregnant women with spontaneous preterm labour between 28 and 36 completed weeks of gestation. Preterm labour was defined as the onset of regular painful uterine contraction linked to progressive cervical change, before the 37 completed weeks of pregnancy. The control group consisted of 100 similar, non-labouring pregnant women with comparable gestational age to the women who were studied and delivered at term between the 37 and 40 weeks of gestation. Participants who had known causes of preterm labour including multiple pregnancy, premature rupture of membranes, placenta previa, cervixial incompetence, anomalies of the uterus, polyhydramnios, anomalies of the fetus, hypertensive disorders of pregnancy, diabetes mellitus, anaemia, infections or receiving magnesium-containing medications were excluded from the study.

A detailed clinical history was obtained from all the participants including their age, parity, socioeconomic status, gestational age, obstetric history, and ante-natal complications. The gestational age was verified using last menstrual period and first trimester ultrasonography wherever feasible. General physical and obstetric examinations were conducted and routine antenatal investigations reviewed to exclude the possibility of confounding conditions.

Using venous blood samples, serum magnesium levels were estimated. In the study group, samples were taken when the patients were admitted before tocolytic or magnesium therapy was started. Blood samples were taken in the control group during routine antenatal visits. Approximately 3 ml of venous blood was collected using aseptic precautions from the antecubital vein, into a plain vacutainer. Care was taken to avoid hemolysis since intracellular magnesium release could give a false high value for serum. The samples were allowed to clot and centrifuged and serum was separated for analysis.

Serum magnesium concentrations were measured by the method of Calmagite using Central labs biochemistry. This method is founded on the formation of coloured complex of magnesium and calmagite with alkaline medium spectrophotometrically at 510 nm. Quality control procedures were performed according to laboratory protocol. The normal reference range for serum was used as normal range 1.8-3.0 mg/dL.

All compiled information was then entered into a structured proforma and analyzed with the help of a statistical software. Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as percentages. Comparison between the two groups in their serum levels of magnesium was done by Student's t-test and p-value of less than 0.05 was considered significant.

Observations and Results

A total of 200 pregnant women were included in the study, comprising 100 women with preterm labour and 100 women in the term pregnancy group. The mean age of mothers in preterm labour group were 25.8 ± 4.2 years and 26.1 ± 4.5 years in term group and the difference was not statistically significant ($p = 0.48$). Most of the participants in both groups were in the age group of 21-30 years of which 62.5% were in preterm and 64.0% were in the term group. There was no significant relationship between the age of the mother and the serum level of magnesium within either group. (Table 1)

Table 1: Distribution of Study Participants According to Maternal Age

Age group (years)	Preterm labour (n = 100)	Term pregnancy (n = 100)	p value
≤20	14 (14.0%)	13 (13.0%)	0.48
21–25	32 (32.0%)	33 (33.0%)	
26–30	30 (30.0%)	31 (31.0%)	
>30	24 (24%)	23 (23.0%)	
Mean ± SD	25.8 ± 4.2	26.1 ± 4.5	

With regard to parity, the primigravidae and multigravidae made up 46.0% and 54.0% of the preterm and term groups of labours, respectively and 43.5% and 56.5% respectively. The yearly fluctuations in serum magnesium concentrations

were not significantly affected by parity in either group ($p > 0.05$), suggesting that the level of serum magnesium was not influenced by parity and thus was not a confounded factor. (Table 2)

Table 2: Parity Distribution in Study Groups

Parity	Preterm labour (n = 100)	Term pregnancy (n = 100)	p value
Primigravida	46 (46.0%)	44 (43.5%)	0.61
Multigravida	54 (54.0%)	56 (56.5%)	

Socioeconomic status was measured by the Modified Kuppaswamy scale. Among women in the preterm labour group, 28.5% were in lower class, 34.0% were in upper-lower class, 25.0% in lower-middle class and 12.5% in upper-middle class. The term pregnancy group, on the other hand, had a greater percentage of women from the upper middle class (21.0%) and lower middle class (33.5%), with

fewer women from the lower socioeconomic status. Although women in the lower socioeconomic classes had lower mean serum magnesium levels relative to women of higher socioeconomic classes in both groups, the difference between socioeconomic classes with each group was not statistically significant ($p > 0.05$).

Table 3: Socioeconomic Status Distribution (Modified Kuppaswamy Scale)

Socioeconomic class	Preterm labour (n = 100)	Term pregnancy (n = 100)
Upper	0 (0.0%)	3 (3.0%)
Upper middle	12 (12.5%)	21 (21.0%)
Lower middle	25 (25.0%)	34 (33.5%)
Upper lower	34 (34.0%)	27 (27.0%)
Lower	28 (28.5%)	15 (15.5%)
Total	100 (100%)	100 (100%)

The mean gestational age of presentation in the preterm labour group was 32.4 ± 2.1 weeks and mean gestational age of delivery in the term group was 38.6 ± 1.2 weeks. Serum magnesium

concentrations showed a decreasing trend with increasing gestational age in both groups; however, the rate of decrease was more marked in women with preterm labour.

Table 4: Gestational Age at Presentation / Delivery

Parameter	Preterm labour (n = 100)	Term pregnancy (n = 100)	p value
Gestational age (weeks), Mean ± SD	32.4 ± 2.1	38.6 ± 1.2	<0.001

Mean serum magnesium level in the preterm labour group was found to be 1.49 ± 0.09 mg/dL while it was 2.06 ± 0.11 mg/dL in the term pregnancy group. This difference proved to be very highly significant

(t = 56.8, p < 0.001). Serum magnesium values in preterm group were (1.30-1.68mg/dL) and in the term laboratory values were (1.85-2.35mg/dL). (Figure 1)

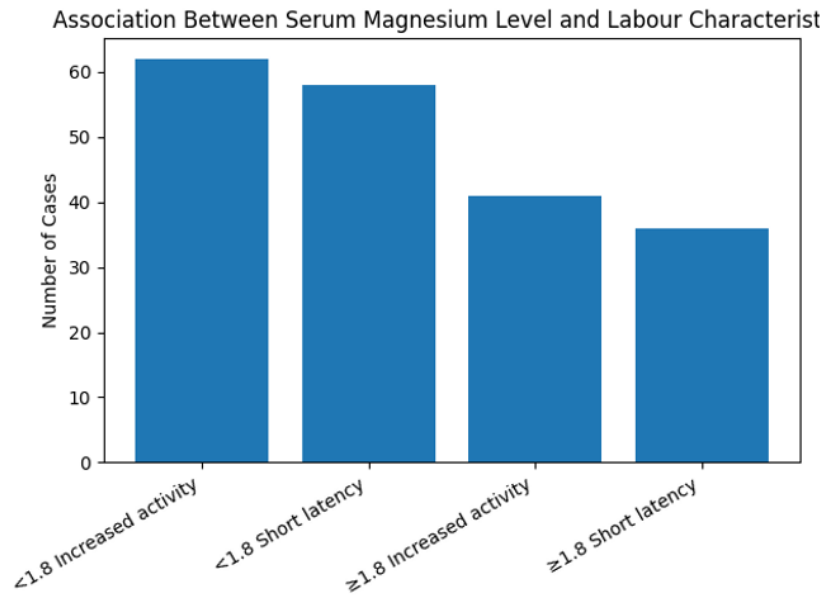


Table 5. Comparison of Mean Serum Magnesium Levels Between Groups

Group	Mean serum magnesium (mg/dL) ± SD	Range (mg/dL)	t value	p value
Preterm labour (n = 100)	1.49 ± 0.09	1.30–1.68	56.8	<0.001
Term pregnancy (n = 100)	2.06 ± 0.11	1.85–2.35		

When the serum levels of magnesium were categorized, hypomagnesemia (serum magnesium <1.8 mg/dL) was found in 61.0% of women in the preterm labour group, compared to 29.5% in the term group. In contrast, normal serum magnesium

levels occurred in 39.0% of the preterm group and 70.5% of the term group. This distribution was statistically significant (chi 2 = 42.6, p < 0.001), showing a strong association between hypomagnesemia and preterm labour.

Table 6. Distribution of Serum Magnesium Levels

Serum magnesium level	Preterm labour (n = 100)	Term pregnancy (n = 100)	χ ² value	p value
<1.8 mg/dL (Low)	61 (61.0%)	30 (30%)	42.6	<0.001
≥1.8 mg/dL (Normal)	39 (39.0%)	70 (70%)		
Total	100 (100%)	100 (100%)		

Further analysis showed that women with low serum magnesium concentrations of lower than 1.8 mg/dL had a significantly higher frequency of uterine contractions and shorter latency to delivery compared with those women with concentrations of magnesium of greater than or equal to 1.8 mg/dL (p

< 0.01). (Figure 2) No significant correlation was found between serum magnesium levels and maternal age, parity or socioeconomic status reinforcing the independent association between low serum magnesium levels and preterm labour.

Table 7: Association Between Serum Magnesium Levels and Labour Characteristics in the Preterm Labour Group (n = 100)

Serum Magnesium Level	Number of Cases (n=100)	Increased Uterine Activity n (%)	Short Latency to Delivery n (%)	p-value
<1.8 mg/dL	61 (61%)	49 (80.3%)	46 (75.4%)	<0.01
≥1.8 mg/dL	39 (39%)	13 (33.3%)	11 (28.2%)	
Total	100 (100%)	62 (62%)	57 (57%)	

Discussion

Preterm labour is a major cause of neonatal morbidity and mortality and the discovery of simple and cost-effective predictive markers is a priority in maternal and obstetric practice. The present study assessed serum magnesium level as a predictive tool for preterm labour and showed significant difference between serum magnesium level in women presenting with preterm labour and those delivered at term. These findings strengthen the increasing body of evidence for a close relationship between hypomagnesemia and preterm labour [1].

In the present study, the mean serum magnesium level of the preterm labour group (1.49 ± 0.09 mg/dL) was significantly lower than that found in the term pregnancy group (2.06 ± 0.11 mg/dL) with a highly significant p value ($p < 0.001$). This observation is in good accord with the results by Anand et al. who found significantly decreased levels of serum magnesium in women with preterm labour regardless of their socioeconomic status [1]. Similarly, Begum et al. reported a significant decrease in serum levels of magnesium in women suffering from preterm labour compared to term deliveries thus supporting the hypothesis of the role of magnesium deficiency in the hyperactivity of the uterus. [2]

The finding of low serum magnesium levels in mothers and preterm labour in this study is similar to other reports by Okunade et al in which hypomagnesemia was shown to be a significant risk factor for spontaneous preterm labour in their cohort [3]. The physiological basis of this association is the magnesium's action as a natural calcium antagonist, which helps to regulate the excitability of myometrial cells and the contractility of uterine muscle. Reduced levels of magnesium may lead to an increased amount of calcium flowing into the cell which causes increased uterine contractions and cervical changes, precipitating preterm labour.

In the present study, hypomagnesemia (serum magnesium < 1.8 mg/dL) was found in 61.0% of women with preterm labour, as compared with 29.5% in the term group. This statistically significant difference further adds to the case of serum magnesium estimation as a screening tool. Comparable proportions have been reported by Meena and Maheshwari who reported a significantly higher prevalence of hypomagnesemia among women with preterm labour irrespective of age,

parity, and socioeconomic status [5]. The similarity in findings despite a larger sample size in the present study adds to the strengthening of the external validity of the present observations.

There has also been some prospective evidence reported for the predictive role of serum magnesium. A prospective cohort study of serum magnesium concentrations between 24 and < 37 weeks of gestation produced moderate sensitivity and specificity for the prediction of spontaneous preterm delivery on the basis of defined values for the cutoff of magnesium concentrations [4]. The present study supports these results showing that women with lower serum magnesium values had an increased frequency of uterine activity and a shorter time to delivery especially when serum magnesium levels fell below 1.8 mg/dL.

Socioeconomic status (obtained from Modified Kuppaswamy scale) had a higher proportion of women in the preterm labour group in the lower socioeconomic strata. Although mean serum magnesium levels were relatively lower in women from lower socioeconomic classes, no statistically significant relationship between socioeconomic status and serum magnesium levels was observed in women of each group. These findings are similar to those of Anand et al, who also found that socioeconomic status was not associated as an independent factor with serum magnesium levels and therefore may be an independent biochemical risk factor for preterm labour. [1]

Parity and maternal age did not have a significant relation with serum magnesium concentrations in the present study. This observation agrees with the rest of research (Venkatesan and Mallika, 2004 and Rajakumari et al. 2011) which found that decreased serum magnesium levels associated with preterm labour were independent of maternal age and parity. [7,8] These consistent results across several studies suggest that the serum magnesium estimation may be a universal method in different obstetric sub-groups.

The clinical importance of serum estimation of magnesium is further supported by studies which have highlighted its association with labour characteristics and adverse pregnancy outcome. Ferdous et al. and Mahboobunnisa et al. reported that decreased serum magnesium levels correlated with increased labour complications and poorer perinatal outcome emphasizing possible therapeutic

implications of early detection [6,9]. In the present study, women with serum magnesium concentrations <1.8 mg/dL had significantly higher uterine activity and shorter course to delivery, supporting the prognostic importance of the serum magnesium concentration.

Advanced analytical methods, including predictive modelling, have shown that serum magnesium concentration can be used to provide an increased prediction of preterm labour when used with clinical variables [11]. While the present study did not use the application of predictive modelling, the strong statistical association noted does suggest that serum magnesium may also be added to routine antenatal screening protocols, especially in resource-limited environments where more sophisticated forms of predictive test may not be possible.

Finally, results of systematic reviews and/or meta-analyses have repeatedly shown an inverse association between maternal magnesium levels and the risk of preterm birth [13]. Zhang et al. concluded that low magnesium status is an important and significant risk factor for preterm birth, thereby giving further validation to the biological plausibilities and clinical relevance of the present findings [13]. Adesola et al. also reported an association between low serum magnesium levels and poor pregnancy outcomes [preterm delivery] which strengthens the need to pursue additional studies involving large numbers of patients. [14]

The present study does have some limitations that need to be taken into account when interpreting the findings of this study. First, despite adequate sample size and equal distribution between the two groups (preterm and term), the study was undertaken in a single tertiary care centre, and thus the generalizability of the findings to other populations should be considered. Second, serum estimation of magnesium reflects only the extracellular, possibly not absolutely accurate, concentration of magnesium and may not be a good measure of total body and intracellular magnesium status, which could have a more direct effect on myometrial activity. Third, serum magnesium levels were measured at one time point; serial measurements throughout gestation may have given us more insight into temporal trends associated with onset of preterm labour. Additionally, dietary intake of magnesium and other micronutrients was not assessed which may have influenced serum magnesium levels.

Conclusion:

The present study shows that there is a significant association of low maternal serum magnesium and preterm labour. Women presenting with preterm labour had significantly lower serum magnesium concentrations than those who delivered at term independent of maternal age, parity and

socioeconomic status. These findings support the role of serum magnesium estimation as a simple, cost-effective and clinically useful predictive tool for identifying women with increased risk of preterm labour. Incorporation of serum levels of magnesium into routine antenatal assessment may aid early recognition, more intensive surveillance and early treatment which could reduce the burden of preterm birth and its related neonatal morbidity.

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