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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 13 (7): 335-339, 2010
ISSN 1028-8880

The Relationship Between Maternal Serum Magnesium Level and Preterm Birth

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Abstract: The aim of this study was to evaluate the relationship between maternal serum magnesium levels and preterm birth. This Nested case-control study carried out on 20 with preterm birth and 20 women at term birth at Imam Khomeini Hospital in Sari/Iran in 2008. The women with singleton gestation and intact fetal membrane suspected to preterm labor (case group), 10 cc blood samples were drawn into syringes and sent to laboratory of the hospital immediately. Sampling for control group was same as the case group. These samples recognized as control group just as birth occurring after week 37. Finally, serum magnesium level measured. Data analyzed using χ^2, t- test and OR (Odd's Ratio). There was a relationship between the number of prenatal visits ($p = 0.008$) and stressful events associated with preterm birth ($p<0.02$). Serum magnesium level was associated with preterm birth OR = 4.75, CI 95% = (0.48-46.91), Sensitivity, specificity, positive and negative predictive value of serum magnesium for preterm birth was 95, 50, 66.5 and 83.33%, respectively. Although, there was a correlation between serum magnesium levels and preterm birth, due to methodology of the study, a cohort study with the same cut off point and supplementation of magnesium in RTC studies is recommended.

Key words: Preterm birth, maternal, serum magnesium, nested case- control

INTRODUCTION

Preterm birth is one of the obstetric problems that was defined as birth occurring after 22 weeks of gestational age and before 37 weeks. Preterm birth occurs in about 10% of entire deliveries (Cunningham *et al*., 2005). Preterm birth is a major cause of neonatal mortality with the highest rates of health care costs due to hospitalization of woman with preterm labor and the expenses of long-term care of preterm birth (Terzidou and Phillip, 2002; McLaurin *et al*., 2009). In addition, prevention of disabilities due to preterm birth is very important for the Neonatalogists (McFarlin, 2009). During the recent years, concerning the related causes and early prediction of preterm labor has increased significantly (Pryde and Mittendorf, 1999; Mittendorf and Pryde, 2005). Some related factors and predictive index of preterm labor are included: Fibronectin (Kiefer and Vintzileos, 2008), risk scoring system, length, dilatation and score of cervix (Crane and Hutchens, 2008; Fuchs *et al*., 2004; Newman *et al*., 2008), βHCG (Khani and Khalilian, 2005; Khani, 2004), salivary estriol (Heine *et al*., 2000) and clinical findings (Yoneyama *et al*., 2009; Macones *et al*., 1999).

With regard to mechanism of action of Magnesium Sulfate to inhibit uterine contractility and using to prevent preterm labor (Fomin *et al*., 2006; Kamal *et al*., 2003), this hypothesis suggests that Magnesium Sulfate may play a role to predict preterm labor in women with decreased serum magnesium level (Macones *et al*., 1999; Fomin *et al*., 2006; Kamal *et al*., 2003; Arikan *et al*., 1999; Wójcicka-Jagodzińska *et al*., 1998). A number of previous studies found a correlation between level of maternal serum magnesium reduction and preterm labor (Smolarczyk *et al*., 1997). Some other studies found no relationship between the two variables.

Considering a few literatures and controversies on correlation between serum magnesium level and preterm labor, we decided to evaluate the relationship between Maternal Serum Magnesium Levels and premature birth. We hope the results of this study could help us to identify the exact correlation between serum magnesium

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levels and premature birth in women at high risk for preterm birth to be a valuable marker for predicting preterm onset of labor and decrease health care costs.

MATERIALS AND METHODS

This study was approved by the ethics committee and financially supported by the research council of Mazandaran University of Medical Sciences in 2008 and written informed consent was obtained from those agreeing to take part in the study.

This Nested case- control study included 40 pregnant women: 20 preterm labor (at least 8 uterine contractions during one hour) (the case group) and 20 at term birth (the control group) who attended in Imam Khomeini Hospital in Sari/ Iran in 2009. Determining the sample size was based on confidence coefficient 95%, Power (1-β) 80% and mean serum magnesium level 0.64% in case group and 0.7% in control group. Also SD = 0.07 and SD = 0.23 mmol dL^{-1} was used in case and control group, respectively. A questionnaire including demographic data, gestational age and history of preterm birth was completed.

All subjects of the studied groups included pregnant women with singleton gestations and intact fetal membranes who admitted in birth room of the hospital due to premature labor (before 37 weeks of gestation). Blood samples from the ulnar vein were drawn into plain tubes prior to every intervention (especially before magnesium sulfate administration) and sent to laboratory of the hospital immediately. The blood samples were kept at 37°C for 1 h. Then the blood samples were centrifuged by 1500 rmp for 2 min the serum was harvested and freezed. Just women with preterm birth were considered as positive cases (case group). If labor pain was stopped and pregnancy continued, the blood sample discarded and the patient was excluded.

The control group consisted of pregnant women with the same gestational age and parity who referred to the prenatal care department of the hospital for achieving prenatal care or other causes excepting premature labor. In addition, only women whose birth occurred after 37th week considered as a control group. Blood samples were taken and examined same as the case group. In both groups, women with IUGR, multiple pregnancies, history of premature labor and preeclampsia were excluded. To identify IUGR, weighting the neonates was performed based on Alexander table from the obstetric text; Williams and Obstetrics (Cunningham *et al*., 2005). An obstetrician confirmed existing of eclampsia.

Venous blood samples (case and control) were frozen at -20°C until all 40 subjects were detected (20 cases and 20 controls groups). Then serum magnesium sulfate were measured by the method of atomic absorption by 4 different concentrations of fresh standard samples prepared by magnesium stock solution (1000 ppm) and a part of calibration grafted. After that, middle glycerol solution 5 and 10% prepared and the serum samples of the both groups were thawed at room temperature. After thawing, 1 cc of each thawing serum samples were transferred to a 5 cc jugs' balloons and diluted with middle glycerol solution. Finally, atomic absorption of magnesium sulfate was calculated by spectrophotometer set (Nicoll *et al*., 1999). Data were analyzed using SPSS 16 software. The correlation between serum magnesium level and preterm labor was assessed by OR. The rest of the data was analyzed using descriptive statistics (frequency, mean and table) and analytical statistics (χ^2, Fisher exact test and t-test). The efficacy of magnesium sulfate for predicting preterm birth (specificity, sensitivity, positive and negative predictive value) was calculated and the cut off point for magnesium sulfate was determined Using SPSS16 software and demonstrated by ROC Curve (Fig. 1).

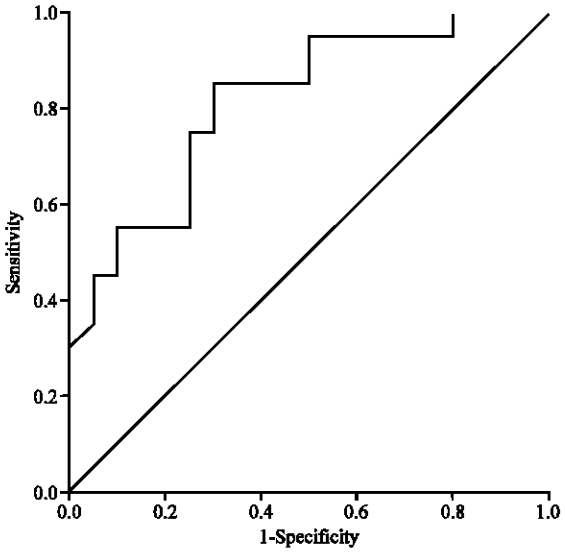

Fig. 1: ROC curve of cut off point for serum magnesium sulfate level in preterm birth. Diagonal segments are produced by ties

RESULTS

The mean and standard deviation (X±SD) of age in case and control groups was 24.4±4.03 and 26.15±6.54, respectively that was not statistically significant between the two groups (p = 0.3). The number of pregnancies (p = 0.51), number of previous abortions (p = 0.2), number of parities (p = 0.7) were similar in both groups. One

Table 1: Frequency distribution of individual and demographic characteristics in case and control groups

	Groups		
Variables	Control	Case	p-value
Age (X±SD)	26±6.54	24.4±4.03	0.3
Socioeconomic status			
Good	1 (5)	0	>0.5
Moderate	17 (85)	90 (18)	
Bad	2 (10)	10 (2)	
Education level			
Illiterate	1 (5)	1 (5)	>0.05
> Diploma	9 (45)	12 (60)	
Diploma	10 (50)	6 (30)	
University	0	1 (5)	
Employment			
Housewife	17 (85)	18 (90)	0.8
Employed	3 (15)	2 (10)	

Values in brackets indicate percentage

participant in control group was found to be in high socio-economic group and two in both case and control groups were in low socio-economic group. There were no differences between case and control groups regarding socio economic status. The education level was not significant in the case and control group (one illiterate in case group and one graduated in control group). Eighteen (90%) in case and 17 (85%) in control group were homemakers. There was no significant difference in employment status between the two groups (p = 0.8) (Table 1).

Previous poor outcome of pregnancy was seen in 4(20%) women of cases and 1(5%) of control group, that the differences were significant in the two groups OR = 4.75, CI 95% = (0.48-46.91). Low birth weight (LBW<2500 g) was observed in 16 (80%) cases and 7 (35%) of controls' newborns that the differences were statistically significant (OR = 7.43, CI 95% = (1.78-31.04).

Perinatal care, less than 5 times was taken to 30% of cases and all participants in control group received perinatal care more than 5 times. There was a significant difference in number of prenatal visit between the two groups (OR = 7.43, CI 95%) = (1.63-3.63).

Five women (25%) in case group and two (10%) in control group had experienced stressful events (such as relatives' death, loss of spouse job, divorce and so on). There was no significant difference in stressful events between the two groups (OR = 39, CI 95%) = (0.51-17.74) (Table 2).

Using SPSS16 software and ROC curve (Fig. 1), the cut off point for magnesium sulfate was 4.7 mg dL^{-1}. Serum magnesium sulfate level was lower than the cut off point in 19 women in case and 10 in control group as specificity, sensitivity, positive and negative predictive values were 95, 50, 66.5 and 83.33%, respectively. Serum magnesium sulfate level was different significantly in both groups (p<0.0001) (Table 3).

Table 2: Frequency distribution of obstetrics and medical characteristics in case and control groups

	Groups		
Variables	Control	Case	p-value
No. of pregnancy			
1	14 (70)	12 (60)	0.51
≤2	6 (30)	8 (40)	
History of abortion			
Yes	18 (90)	15 (75)	0.2
No	2 (10)	5 (25)	
Parity			
0	14 (70)	15 (75)	0.7
≤1	6 (30)	5 (25)	
History of poor outcome pregnancy			
Yes	1 (5)	4 (20)	0.15
No	19 (95)	16 (80)	
LBW			
Yes	7 (35)	16 (80)	0.004
No	13 (65)	4 (20)	
No. of prenatal care visits			
<5	0 (0)	6 (30)	0.008
≤5	20 (100)	14 (70)	
History of stressful events during current pregnancy			
Yes	2 (10)	5 (25)	0.02
No	18 (90)	15 (75)	

Values in brackets indicate percentage

Table 3: Frequency distribution of samples in both case and control group according to serum magnesium level-Sari 2008

	Groups		
Magnesium level	Control	Case	p-value
<46.7 mg dL^{-1}	19 (95)	10 (50)	0.0001
>46.7 mg dL^{-1}	1 (5)	10 (50)	
Total	20 (100)	20 (100)	

Values in brackets indicate percentage

DISCUSSION

This study revealed a correlation between maternal serum magnesium level and preterm labor. Namely, if the serum magnesium level decreases, preterm labor will be predictable in next weeks (p<0.0001). There are controversies in this regard. Some studies has been found a correlation between the two variables (Yoneyama *et al*., 2009; Macones *et al*., 1999; Fomin *et al*., 2006; Kamal *et al*., 2003) that was similar to our findings, while other studies had found no relationship between them (Arikan *et al*., 1999; Wójcicka-Jagodzińska *et al*., 1998; Smolarczyk *et al*., 1997; Nicoll *et al*., 1999; Akoury *et al*., 1997; Reynolds *et al*., 2000; Takaya *et al*., 2006; Kumar *et al*., 2002). In addition, a recent systematic review revealed that using magnesium sulfate had no effect on delaying the preterm labor or prevention of premature birth (Smolarczyk *et al*., 1997). Although the inhibitory mechanism of magnesium sulfate ($MgSO_4$) on uterine contractility seems obvious, there are differences in individual metabolism of different materials.

Meanwhile, the exclusion criteria considering in present study were omitted or not considered by some other studies. Similar to Kamel's study (Macones *et al*.,

1999), we found no significant difference in age, number of pregnancies, history of miscarriage, education level, employment status and socio-economic condition between the case and control groups. Whereas, it was claimed that there is a relationship between preterm labor and maternal ages, low economy and employment status (Cunningham *et al*., 2005), that was not similar to our result. Sampling were obtained only from governmental hospitals but not private ones, in which participants were in similar socioeconomic status or the same in other variables and maybe this is the cause of different results.

In this study, stressful conditions in present pregnancy, number of prenatal visits and LBW had been correlated with preterm labor. These findings are confirmed by Cunningham *et al*. (2005). It is believed that association of stressful events with releasing catecholamine and increasing corticosteroids can lead to increase uterine muscle contraction. On the other hand, one of the aims of prenatal visits is decreasing preterm labor and LBW (Cunningham *et al*., 2005). Administration of magnesium supplement in hypomagnesaemia women will prevent many of undesirable events during fetal, neonatal and adulthood period, if the correlation is confirmed in future studies (cohort and clinical trial). Besides, according to Barker's hypothesis, there is a relationship between IUGR and metabolic syndrome and many other diseases in adult age. So that, assuming correlation between serum magnesium sulfate level and LBW, less number of prenatal cares is associated with more preterm labor and LBW.

Since, this is a Nested case- controls study, it cannot verify the correlation between Serum magnesium sulfate level and preterm labor yet. So, a cohort study is recommended with the same cut off point for magnesium sulfate in which confounder variables would have been controlled and identified prospectively. Namely, a correlation between Serum magnesium sulfate level and preterm labor has not been determined yet. Since there is no Meta analysis in previous analytic studies, we recommend Meta analysis on existence cohort studies. In addition, since the cut off point for magnesium sulfate was not clear at the time of study, performing the survey by Nested case- control method was requisite.

ACKNOWLEDGMENT

This study was approved by the ethics committee and financially supported by the Research Council of Mazandaran University of Medical Sciences by grant No. 8415 due to proposal of pharmaceutics' student.

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