Indian Journal of Obstetrics and Gynecology Research 2020;7(3):356–363

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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ipinnovative.com

Original Research Article

Serum magnesium level as a predictive tool for preterm labour

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ARTICLE INFO

Article history:
Received 17-02-2020
Accepted 23-04-2020
Available online 12-09-2020

Keywords:
Preterm
Serum magnesium level
Term delivery
Parameter

ABSTRACT

Introduction: 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. Spontaneous preterm labor that is labor before 37 weeks of gestation is the main cause of preterm delivery. With increasing gestation the level of Serum magnesium levels decreases.

Materials and Methods: A case-control study was carried out to evaluate serum magnesium levels and associated symptoms in women with preterm labour (28-36 weeks) and compare them with patients in same gestational age who delivered at term (37-40 weeks).

Results: Women in preterm labour had a significantly reduced serum magnesium level (mean 1.466 mg/dl with a S.D. of 0.077 versus 2.083 mg/dl with a SD of 0.105) for those delivered at normal magnesium levels.($p<0.05$).

The serum Magnesium level of preterm patients ranged from 1.32 to 1.60 mg/dl with mean Magnesium level of 1.466 ± 0.077 S.D. In normal pregnant women it ranged from 1.85 to 2.36 mg/dl with a mean Magnesium level of 2.083 ± 0.105 S.D which was highly significant ($p<0.00001$). The difference of serum Magnesium levels observed between the study population and control population is independent of factors like maternal age, parity, socio-economical status.

Conclusion: The present study revealed significantly lower levels of serum magnesium in patients with preterm labour without any apparent cause as compared to normal pregnant women in labour. Hence, estimation of serum magnesium levels in pregnancy may be a useful parameter in preterm labour. The results of the present study add to the existing evidence that low serum magnesium level may be a risk factor for preterm labour.

1. Introduction

Preterm labour is defined as labour occurs with regular, and frequent uterine contractions causing progressive cervical changes before 37 completed weeks of gestation.[1] It accounts for 10-15% of all pregnancies. Preterm delivery is not only a leading cause of neonatal morbidity and mortality;[2,3] its long-term sequelae pose a serious problem for the offspring and for the mother.[4]

The cause of preterm labour is not yet completely known; in 50% cases it is spontaneous and idiopathic, although several potential risk factors have been identified. The main one among them is premature rupture of membrane (PROM), and others are multiple pregnancy, hypertensive disorder of pregnancy, infection, cervical incompetence, antepartum hemorrhage, fetal and uterine anomalies, anemia, heavy work, smoking etc. It is also related to socioeconomic status and geographic location.[5–7]

Prevention of viable spontaneous preterm birth through screening is one of the key aims of antenatal care as these have implications for child, mother, and society. If women can be identified to be at high risk in early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions (primary prevention). However,

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https://doi.org/10.18231/j.ijogr.2020.077

the disease mechanisms behind these problems are not well understood. Consequently, tests for their prediction and treatments for their prevention are not well developed. Clinically, it would be useful to be able to predict who will deliver preterm. The predictors may be used in the management of women at high risk for preterm labour such as women with previous preterm labour and also can be used as a part of a management protocol to individualize patient care.[8,9]

In line with different suggested etiologies a change in cellular basic biochemical function caused by a change in micro and macro minerals is also proposed.[10] Although these trace elements do not play any direct role in the etiology of preterm labor, they may have an indirect role in the etiopathogenesis of preterm labor.[11] Among the trace elements, magnesium has received the highest attention.[12] Decreased serum magnesium level could probably decrease the magnesium level in myometrium which could lead to uterine hyperactivity followed by cervical dilatation.[13,14]

In the women with preterm labor, the most beneficial intervention is antenatal corticosteroids. Corticosteroids have been proved to reduce neonatal mortality and morbidity.[15] The main goal of tocolytic therapy is to maintain the pregnancy for at least 48 hours, which provides time for administration of antenatal corticosteroids.

In this study, we aimed to evaluate serum magnesium level in women with gestational age of 26-32 weeks and signs of preterm labor, and compare it with serum magnesium level in women with normal pregnancy of the same age. We also aimed to assess the effect of $MgSO_4$ as a tocolytic agent in delaying labor for at least 48 hours and to evaluate the relationship between serum magnesium level and response to $MgSO_4$.

1.1. Role of magnesium in causing preterm labour

Magnesium deficiency is not readily detectable as less than 1% of the total body magnesium is found in the plasma and red blood cells[16,17] moreover, ionized magnesium assays are non-routine and expensive.[18] Studies from different regions report a decline in magnesium levels during pregnancy[19,20] with values reaching their lowest point at the end of the first trimester.

Since magnesium has an inhibitory role on myometrial contractions, attention has been paid to the role of magnesium deficiency in causing preterm labour. The inhibitory effect of magnesium on preterm labour contractions is attributed to antagonism of calcium mediated uterine contractions.[21]

The regulatory pathway leading to uterine contraction begins with an increase in the intracellular free calcium concentration, which activates myosin light chain kinase (Mizuki and Associates, 1993). High concentrations of extracellular magnesium have been reported not only to inhibit calcium entry into myometrial cells but also to lead to high intracellular magnesium levels. This later effect has been reported to inhibit calcium entry into the cells presumably by blocking calcium channels.[22] Hence, hypomagnesemia leads to neuromuscular hyperexcitability resulting in muscle cramps and uterine hyperactivity. The hyperexcitability of uterine musculature induced by hypomagnesemia leads to increased cervical dilatation which in turn facilitates approach of vaginal micro-organisms into cervical canal and changes quality and quantity of vaginal discharge while uterine passage is being colonized by pathogenic micro-organisms.[23]

2. Materials and Methods

It is a prospective case control study conducted in Department of Obstetrics and Gynaecology in 2017-2018.

Categorization of cases: A complete clinical history regarding age, socioeconomic status, history of present illness, past illness and family history is taken.

A detailed obstetrical history particularly antenatal care and history of previous pregnancy in multigravida are recorded. Cases are studied in to two groups:

There are 100 cases in each group.

2.1. Control group

The control group comprised all the cases attending outdoor patient with normal pregnancy of different trimester.

2.2. Study group

This group comprised the women having preterm labour (Between 28-37 weeks).

The study protocol went as follows:

1. To determine the serum Magnesium concentration in women with preterm labour between 28-36 wks of gestation and compare the results with those obtained from pregnant women of same period of gestation not in labour.
2. To correlate magnesium status of women in preterm labour between 28 to 36 weeks of gestation with indices such as age, parity and gestational age.

Following investigation were carried out:

1. Blood examination: Hemoglobin in gm%, blood sugar, HIV, HBsAg, VDRL, PT INR, Blood group and blood urea level.
2. Urine examination: Albumin, sugar and microscopic.

Care is taken not to administer any magnesium containing compound prior to the estimation.

2.2.1. Method of collection of samples for the estimation of serum magnesium levels

Blood samples taken from patients in Group I (preterm) were collected at the time of admission to the labour ward,

while as blood samples from the patients in Group II (normal) were collected in the outpatient department. They were followed up till delivery.

2.2.2. Samples hence collected were carried in 3 ml of venous blood was taken from antecubital vein in a dry vial with disposable syringe and needle.

2.2.3. Method of determination of magnesium

All tests were carried out in central laboratory, department of biochemistry, RNT medical college, Udaipur by Calmagite method.

Calmagite method (For the determination of Magnesium in serum)

(Gindler, E. et. al. (1971), Clin. Chem. 17: 662)

Magnesium +Calmagite $\frac{alkaline}{medium}$ Red coloured complex

Normal reference values

Serum (Adults):1.8-3.0mg/dL

Reagents

L1: Buffer Reagent

L2: Colour Reagent

S: Magnesium Standard (2.44mg/dL)

Storage Istability

Reagents are stable at 2–8^{0}C till the expiry mentioned on the label.

2.3. Reagent preparation

Reagents are ready to use. Protect from bright light. Working reagent: For larger assay series a working reagent may be prepared by mixing equal volumes of L1 (Buffer Reagent) and L2 (Colour Reagent). The working reagent is stable at 2-8^{0}C for at least one month. Keep tightly closed.

2.4. Sample material

Serum (Free from hemolysis) RBC's have double the magnesium content compared to serum, and hence hemolysed samples should not be used. Magnesium is reported to be stable in serum / plasma for 7 days at 2-8'C.

2.5. Procedure

Wavelength/filter: 510 nm(Hg 546 nm) / Green

Temperature: Room temperature (25^{0}C)

Light path: 1 cm

Pipette into clean dry test tubes labelled as Blank (B), Standard (S), and Test(T)

Addition sequence	B (ml)	S (ml)	T (ml)
Buffer Reagent(L1)	0.5	0.5	0.5
Colour Reagent(L2)	0.5	0.5	0.5
Distilled water	0.01		
Magnesium Standard (S)		0.01	
Sample			0.01

Mix well and incubate at R.T. (25°C) for 5 min. Measure the absorbance of the Standard (Abs.S), and Test Sample (Abs.T) against the Blank, within 30 Min.

Calculations

Magnesium inmg/dl= $\frac{Abs.T}{Abs.S} \times 2.44$

2.6. Statistical analysis

Data were expressed as mean±SD (standard deviation). For statistical analysis students't' test, chi-square test was used. 'P' value of <0.05 was considered as significant as <0.001 was considered as highly significant.

3. Observation

Table 1: Serum magnesium level in relation to age Normal pregnancy (n=100)

S. No.	Age (years)	No. of Case	Average Serum Magnesium Level (mg%)
1.	15-20	20	2.0871
2.	21-25	43	2.0848
3.	26-30	34	2.0906
4.	30-35	3	2.0939

Table 2: Serum magnesium level in relation to age preterm case (n=100)

S. No.	Age (years)	No. of Cases	Average Serum Magnesium Level (mg%)
1.	15-20	28	1.468
2.	21-25	46	1.467
3.	26-30	21	1.466
4.	30-35	35	1.468

Table 3: Serum magnesium level in relation to parity normal pregnancy (n=100)

S. No.	Parity	No. of Cases	Average Serum Magnesium Level (mg%)
1.	0	35	2.085
2.	1	28	2.084
3.	2	22	2.090
4.	3	14	2.091

Table 4: Serum magnesium level in relation to parity preterm case (n=100)

S. No.	Parity	No. of Cases	Average Serum Magnesium Level (mg%)
1.	0	46	1.468
2.	1	33	1.468
3.	2	16	1.467
4.	3	5	1.470

Table 5: Serum magnesium level in relation to socioeconomic status normal pregnancy (n=100)

S. No.	Socio-economic status	No. of Cases	Average Serum Magnesium Level (mg%)
1.	I	24	2.087
2.	II	32	2.089
3.	III	24	2.086
4.	IV	12	2.088
5.	V	8	2.095

Table 6: Serum magnesium level in relation to socioeconomic status preterm cases (n=100)

S. No.	Socio-economic status	No. of Cases	Average Serum Magnesium Level (mg%)
1.	I	24	1.465
2.	II	31	1.467
3.	III	25	1.467
4.	IV	12	1.472
5.	V	8	1.478

Table 7: Serum magnesium in normal pregnancy 1st trimester (6-12 weeks)

S. No.	Case No.	Duration of pregnancy (weeks)	Serum magnesium level (mg%)
1	1	12	2.15
2	2	10	2.3
3	3	12	2.15
4	4	12	1.96
5	5	8	1.98
6	6	12	2.2
7	7	6	2.14
8	8	12	2.16
9	9	8	1.98
10	10	8	2.01
11	11	6	2.18
12	12	8	2.24
13	13	8	2.18
14	14	8	1.98
15	15	10	2.16
16	16	12	2.3
17	17	8	2.18
18	18	8	2.26
19	19	8	2.06
20	20	12	2.2
21	21	8	1.92
22	22	10	2.16
23	23	8	2.11
24	24	10	2.06
25	25	8	2.12
26	26	8	2.16
27	27	8	2.12
28	28	10	2.14
29	29	12	1.96
30	30	12	2.06
31	31	8	2.2
		Mean±SD	2.1219±0.1017

Table 8: Serum magnesium in normal pregnancy 2^{nd} trimester (13-24 weeks)

S. No.	Case No.	Duration of pregnancy (weeks)	Serum magnesium level (mg%)
1	32	20	1.92
2	33	20	2
3	34	16	2.22
4	35	16	2.36
5	36	20	2.2
6	37	20	1.96
7	38	16	2.14
8	39	16	2.05
9	40	16	1.99
10	41	20	1.92
11	42	20	2.21
12	43	14	2.15
13	44	16	2.14
14	45	20	1.96
15	46	18	1.99
16	47	16	2.15
17	48	24	1.99
18	49	16	2.2
19	50	20	1.98
20	51	16	2.05
21	52	18	2.12
22	53	20	1.96
23	54	24	2.1
24	55	24	2.1
25	56	20	2.06
26	57	18	2.16
27	58	16	2.13
28	59	16	2.02
29	60	20	1.98
30	61	24	2.15
31	62	24	2.03
		Mean±SD	2.0770± 0.1048

4. Dissscusion

The cause of preterm labour is not yet completely known, although some risk factors have been identified recently, but none completely explain all preterm labour. However recently, involvement of magnesium in many physiological and pathological processes has been clearly verified. There are several studies and reports concerning the evidence of low magnesium in serum causes for preterm labour.

The main focus of this study is serum magnesium level in preterm labour and its relation with the etiology of preterm labour. When compared with the term labour, the serum magnesium concentration is found as markedly reduced in preterm labour.

In this study the mean magnesium was1.466±0.077mg/dl for the patients with preterm labour and 2.083±0.105mg/dl for those with normal pregnancy. The mean difference is found to be statistically significant ($p< 0.05$). This result is also found similar to and supported by the study findings of other investigators. In a study carried out by Puspo and Jagdish (1991).[23] Serum magnesium level in preterm labour was found to be1.67±0.23mg/dl.

Kurzel[24] found that the patients with preterm labour had significantly depressed serum magnesium level and the mean was1.60±0.466. The finding of the present study is also similar to the study result of Rasuand Gupta, who considered the critical level of serum magnesium below 1.8mg/dl, indicated the view of Potnis et al., who also believed that the hypomagnesaemia may play an important role in etiology of preterm labour.[25]

They considered serum magnesium level to be the diagnostic and prognostic value. In a recent study by Kamal et al. also found the mean serum magnesium level in preterm labour cases was 1.4mg/dl±0.22SD and concluded that the estimation of serum magnesium may prove to be a valuable tool in predicting the preterm onset of labour.[12]

Begum et al. also observed that there was significant reduction ($p < 0.001$) of serum magnesium (mean 1.77±0.36) in women with preterm labour. The statistical analysis of the present study shows that the proportion

Table 9: Serum magnesium in normal pregnancy 3rd trimester (25-40 weeks)

S. No.	Case No.	Duration of pregnancy (weeks)	Serum magnesium level (mg%)
1	63	28	2.15
2	64	26	2.25
3	65	28	2.12
4	66	36	1.86
5	67	28	2.15
6	68	28	2.16
7	69	32	1.96
8	70	32	1.99
9	71	28	2.15
10	72	28	2.08
11	73	34	1.98
12	74	28	2.14
13	75	30	1.9
14	76	34	1.96
15	77	32	2.06
16	78	28	2.15
17	79	32	1.99
18	80	36	2.14
19	81	26	2.06
20	82	28	2.25
21	83	36	2.15
22	84	32	1.98
23	85	32	2.11
24	86	34	1.99
25	87	36	1.85
26	88	32	2.15
27	89	28	2.25
28	90	26	2.2
29	91	30	2.16
30	92	32	1.96
31	93	28	2.05
32	94	32	1.96
33	95	36	2.05
34	96	30	2.25
35	97	32	2.01
36	98	30	1.96
37	99	32	2.03
38	100	32	1.99
		Mean±SD	2.0684± 0.1096

Table 10: Comparison of serum magnesium level in preterm labour with normal pregnancy

Group	No. of cases	Serum magnesium level (mg/dl)±S.D.	't' value	P value	Remarks
Normal pregnancy v/s	100	2.0836±0.1057	47.0565	< 0.05	Significant
Preterm labour	100	1.4667±0.0774			

Table 11: Summary of calculation

	Normal pregnancy		Preterm
Mean	2.0836		1.4667
Variance	0.0112		0.006
Stand. Dev.	0.1058		0.0775
n	100		100
t		47.0565	
Degrees of freedom		198	
critical value		1.976	

of low serum magnesium level is high (60%) among the Patients with preterm level compared to normal labour (32%). On the contrary, the proportion of normal serum magnesium was higher (68%)among the pregnancy with normal labour compared to the preterm labour(40%). This was statistically significant ($p<0.001$). [26]

The objective of this study was to formulate a proposition that would help in reducing perinatal mortality and morbidity by preventing preterm birth.

Prophylactic oral magnesium supplementation to the patients with higher risk for development of preterm labour may be successful for prevention of preterm labour, as there may be relative deficiency due to increased demand.

Further studies are required to find out the etiology of irritability of uterus due to low level of serum magnesium, to evaluate the role of magnesium in preterm labour and the probability of use of low serum magnesium as a marker or predictor of idiopathic group of preterm.

5. Conclusion

The cause of preterm labour is not yet completely known, although some risk factors have been identified recently, but none completely explain all preterm labour. However recently, involvement of magnesium in many physiological and pathological processes has been clearly verified. There are several studies and reports concerning the evidence of low magnesium in serum causes for preterm labour.

Some predictive tests for preterm births are used they still have poor sensitivities and are very expensive. Estimation of Magnesium concentrations is relatively cheap.

It may be concluded that estimation Magnesium supplementation may be considered in patients with decreased serum Magnesium levels to prevent preterm labour.

Based on the findings of the current study, serum magnesium level can be used as a predictive tool for preterm labour. It seems serum magnesium evaluation must be carried out in pregnant women in order that high risk preterm labour be predicted and prevented. Measurement of magnesium may also help in the cases of preterm labour to select patients who benefit from $MgSO_4$ as a tocolytic agent.

Future studies are warranted in order to investigate the effect of magnesium supplementation in the patients with decreased serum magnesium level to prevent preterm labour.

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Cite this article: Meena PK, Maheshwari S. Serum magnesium level as a predictive tool for preterm labour. *Indian J Obstet Gynecol Res* 2020;7(3):356-363.