



Association of Vitamin D Deficiency in Preterm Labour and Its Effect on Feto-maternal Outcome

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Abstract

Background: Preterm birth being one of the leading causes of perinatal morbidity and accounts for 5% to 18% of preterm births across the globe. Vitamin D a regulator of cytokines and neutrophil degradation product production and function, prevents microbial invasion and regulates the acquired and innate immune response at fetomaternal interface during antenatal period and maintains a healthy term pregnancy. This study aims to evaluate the association of vitamin D deficiency in preterm labour and to find out its effect on perinatal outcome.

Methods: A prospective case control observational study was conducted in a medical college of Gurugram district of Haryana, North India. Total 150 patients were enrolled (75 in term group and 75 in control group) in the study from the labour room. After complete obstetrical examination and investigations, blood 25(OH)D levels

were measured on the day of delivery . Maternal and neonatal outcome were assessed in relation to the Vit D level.

Results: The incidence of vitamin D deficiency was very high in both group of women. It was slightly more in preterm group (68%) than term group (58.7%). Vitamin D deficiency in women aged less than 25 years was 72.09% in preterm group and 60% in term group. Approximately 81% primigravida and 58.13% multigravidas had preterm births. No antenatal and postnatal complications were seen in women with vitamin D deficiency in preterm group. Neonates born to Vitamin D deficient mothers, 69.67% required NICU admission in the preterm group whereas 52.63% in the term group.

Conclusion: Vitamin D (25hydroxy) level was below normal in a majority of patients in both group of women, delivered at term and at preterm. It was slightly more in

preterm group than the term group but the difference was not statistically significant. No increase in antenatal or post-natal complication observed in women with Vitamin D deficiency. NICU admission was more in the preterm neonates born to mothers with Vitamin D deficiency but prematurity itself is also a risk factor for NICU admission. It makes a point that cut-off taken for Vitamin D level needs to be lowered for Indian women.

Keywords: preterm birth, vitamin D levels, PPRM

Introduction

Preterm birth being one of the leading cause of perinatal morbidity and mortality accounts for 5% to 18% of preterm births across the globe. More than a one million infants die worldwide due to prematurity each year. It is the second leading cause of mortality in under 5 years of age.¹

Infection is found to be one of the important risk factors for preterm birth (40% of the spontaneous preterm births).

Bacterial invasion causes choriodecidual interface infection which leads to cytokine production from maternal and foetal organs and leads to prostaglandin production which triggers the preterm contractions.

Vitamin D a regulator of cytokines and neutrophil degradation product production and function, prevents microbial invasion and thus has an immunomodulatory and anti-inflammatory effect.²

Vitamin D regulates the acquired and innate immune response at feto-maternal interface during antenatal period and maintains a healthy pregnancy.³

In vitamin D deficient women, the production of inflammatory cytokines such as IL-6, TNF α are increased and acts as a physiological pathway in the pathogenesis of preterm labour.

Low vitamin D levels is also labelled to be the cause of complications of pregnancy like premature rupture of

membranes, gestational hypertension, Preeclampsia, gestational diabetes, bacterial vaginitis, prolonged labour, increased risk of caesarean section etc.⁴

Maternal vitamin D deficiency is reported with neonatal vitamin D deficiency leading to poor birth outcomes like foetal hypovitaminosis D, neonatal rickets and tetany, lower respiratory tract infection, low birthweight, neonatal hypoglycaemia, impaired neuro-behavioural development, seizures etc.⁵

Various studies have been done on vitamin D level and its effect on various pregnancy complications like pre-eclampsia, diabetes, caesarean section, small for gestational age etc. But its associated risk for preterm labour is still unclear and not much data is available in Indian literature. Thus, this study aims to fill in the lacunae by evaluating the association of vitamin D deficiency in preterm labour and to find out its effect on perinatal outcome.

Material and Methods

This prospective case control observational study was conducted in the Department of Obstetrics and Gynaecology after ethical committee permission. A total 150 patients (75 preterm and 75 term), who had fulfilled the inclusion criteria, were enrolled from the department labour room, after informed consent, during a period of 18 months.

Inclusion criteria: All pregnant women in established labour between 28-36+6 weeks were included in study group and all the pregnant women with established labour in gestational age more than 37 weeks were included in control group.

Exclusion criteria: women with multiple gestation, patient with cervical incompetence, polyhydromnios, structural uterine abnormalities, antepartum haemorrhage, pregnant women with intrauterine death, pregnancy complicated with medical disorders like

diabetes, chronic renal disease, hepatic failure, jaundice, gastro-intestinal disorders, severe cardiac disorders were excluded from the study.

The gestational age was calculated from first day of last menstrual period and earliest available ultrasound scan. Diagnosis of labour was taken as women who were getting regular uterine contractions of at least 1 in every 10 minutes associated with cervical dilatation of more than equal to 2cm and effacement of cervix more than 50%.

Complete workup was done including history, thorough physical examination and all antenatal investigations and other relevant investigations were reviewed and recorded. After complete obstetrical examination, 5ml venous blood sample was collected for 25(OH)D levels on the day of delivery for the diagnosis of vitamin D deficiency. Outcome of the pregnancy was assessed for maternal and foetal outcome on following points.

Obstetric outcome: Assessed for mode of delivery, Associated obstetric complications, Intrapartum complications, Postpartum complications and 25(OH)D levels on the day of delivery.

Result

Table 1: The overall vitamin D levels in the preterm and term group

Vitamin-D status	Preterm (n-75)		Term (n – 75)		X ²	p-value
	N	%	n	%		
Normal	5	6.7%	10	13.3%	2.243	0.337
Insufficiency	19	25.3%	21	28.0%		
Deficiency	51	68.0%	44	58.7%		
Total	75	100.0%	75	100.0%		

The mean vitamin D level in preterm group was 19.213 and in term was 20.9145. 93.33% women in preterm group and 86.66% women in term group had inadequate vitamin D levels. (Table1)

The overall prevalence of vitamin D deficiency was 63.33% and vitamin D insufficiency was 26.66%. Only 10% of the participants had normal vitamin D levels.

Neonatal outcome: recorded live or still birth, APGAR at 1 and 5 min, Birth weight, Neonatal Intensive Care Unit (NICU) admissions, duration of NICU stay and Neonatal mortality.

In this study the vitamin D levels were categorised to sufficient, insufficient and deficient group and maternal and foetal outcome in relation to different level of vitamin D was analysed. The cut-off value for vitamin D insufficiency was 30ng/dl and deficiency were 20ng/dl.

Result of women with vitamin D deficiency in preterm and term group was compared with result of women with sufficient vitamin D levels in preterm and term group and data analysed statistically.

SPSS software package was used to perform analysis. Measurement data were expressed as mean ± standard deviation. Student t-test was used to compare means between two groups. Analysis of variance was performed in enumeration data. Conditional logistic regression analysis was used to reveal the correlation between 25(OH)D and PTB risk. Significance level was defined as p<0.05.

In the study group (preterm), incidence of vitamin D deficiency was 68% and in control group (term), the incidence was 58.7%. Thus, vitamin D deficiency was higher in women who delivered prematurely. But this difference was not statistically significant. (Table 1)

Table 2: Association of vitamin D levels with the demographic data

Vitamin D status	Parameters							
	18-25 years age				More than 25 years of age			
	Preterm		Term		Preterm		Term	
	N	%	N	%	N	%	N	%
Normal	2	4.65	5	10.00	3	9.37	5	23.80
Insufficiency	10	23.25	15	30.00	9	28.12	13	61.90
Deficiency	31	72.09	30	60.00	20	62.50	3	14.28
Total	43	100.00	50	100.00	32	100.00	21	100.00
Vitamin D status	Primigravida				Multigravida			
	Preterm		Term		Preterm		Term	
	N	%	N	%	N	%	N	%
	Normal	1	3.12	4	10.52	4	9.30	6
Insufficiency	5	15.62	10	26.31	14	32.55	11	29.72
Deficiency	26	81.25	24	63.15	25	58.13	20	54.05
Total	32	100.00	38	100.00	43	100.00	37	100.00

The mean age of preterm group and term group was 25.080 and 24.520 respectively. Vitamin D deficiency in women aged less than 25 years was 72.09% in preterm group and 60% in term group. The vitamin D deficiency and insufficiency was much higher in women who were in the age group of 18-25 years. The overall low vitamin D level was 95.34% in preterm women and 90% in term women in this age group. (Table2)

The overall low vitamin D level were higher in primigravida than multigravida in both preterm and term group. 96.87% out of total 32 primigravida and 90.69% out of total 43 multigravida who had preterm delivery had overall low Vitamin D level. The overall vitamin D deficiency was 89.47% in primigravida and 83.78% in multigravida in the group of women who delivered at term. (Table 2)

Table 3: Association of vitamin D levels with period of gestation

Vitamin D status	28-31+6 weeks		32-33+6 weeks		34-36+6 weeks		37-38+6 weeks		39-40+6 weeks		>41 weeks	
	n	%	n	%	n	%	n	%	n	%	n	%
Normal	0	00.00	2	15.38	3	6.25	3	8.57	7	17.94	0	00
Insufficiency	5	35.71	4	30.76	10	20.83	5	14.28	15	38.46	1	100
Deficiency	9	64.28	7	53.84	35	72.91	27	77.14	17	43.58	0	00
Total	14	100	13	100	48	100	35	100	39	100	1	100

Vitamin D deficiency in late preterm was approximately 73% and early preterm was 59%. In term group, vitamin D deficiency was 77% in early term and 43.58% in late term. The mean gestational age was 34.31 in preterm group and 38.64 in term group. In preterm group the overall low vitamin D level were 100% in women who delivered between 28-31⁺⁶ weeks, 84.61% in women who

delivered between 32-33⁺⁶ weeks and 93.75% in women who delivered between 34-36⁺⁶ weeks. In term group the overall low vitamin D level were 91.42% in women who delivered between 37-38⁺⁶ weeks and 82.05% in women who delivered between 39-40⁺⁶ weeks. No significant relation was observed between vitamin D levels and period of gestation at delivery. (Table3)

Table 4: Association of vitamin D levels with obstetric and neonatal outcome

Vitamin D status	Vaginal delivery				Caesarean delivery			
	Preterm		Term		Preterm		Term	
	N	%	N	%	N	%	N	%
Normal	3	5.88	7	12.72	2	8.33	3	14.28
Insufficiency	9	17.64	16	29.09	10	41.66	6	28.57
Deficiency	39	76.47	32	58.18	12	50.00	12	57.14
Total	51	100	55	100	24	100	21	100

Vitamin D status	Intra natal complications				Postnatal complications			
	Preterm		Term		Preterm		Term	
	N	%	N	%	N	%	N	%
Normal	3	75.00	3	50.00	1	33.33	1	100
Insufficiency	1	25.00	3	50.00	2	66.66	0	00
Deficiency	0	00	0	00	0	00	0	00
Total	4	100	6	100	3	100	1	100

Vitamin D status	Live birth				Still birth			
	Preterm		Term		Preterm		Term	
	N	%	N	%	N	%	N	%
Normal	5	6.75	9	12.16	0	00	1	100
Insufficiency	19	25.67	21	28.37	0	00	0	00
Deficiency	50	67.56	44	59.45	1	100	0	00
Total	74	100	74	100	1	100	1	100

Vitamin D status	NICU admission				Neonatal sepsis			
	Preterm		Term		Preterm		Term	
	N	%	N	%	N	%	N	%
Normal	1	2.32	1	5.26	0	00	0	00
Insufficiency	12	27.90	8	42.10	4	26.66	0	00
Deficiency	30	69.76	10	52.63	11	73.33	2	100
Total	43	100	19	100	15	100	2	100

In preterm group 32% women had caesarean section, out of which 91.66% women had overall low vitamin D levels. Whereas in term group 28% women had caesarean section, out of which 85.71% women had overall low vitamin D levels. Though more women with overall low vitamin level had caesarean section in preterm group than term group but this difference was not statistically significant. (Table4)

No antenatal and postnatal complications were seen in women with vitamin D deficiency in preterm group. No significant difference was found in intra natal and postnatal complications and vitamin D levels between preterm and term levels. (Table4)

Total 43(58.3%) neonates in the preterm group and 19(25%) neonates needed Neonatal Intensive care unit (NICU) admission. Out of these 97.66% neonates in preterm group and 94.73% neonates in term group were born to mother with low Vitamin D levels.

Total 15 neonates in the preterm group and 2 infant in the term group was diagnosed with neonatal sepsis and all of them (100%) were born to mother with inadequate Vitamin D level. (Table4)

Discussion

Vitamin D deficiency during pregnancy has been reported to be associated with many adverse maternal and neonatal outcomes and is increasingly recognized as a public health concern. This study was aimed to find out the association of inadequate vitamin D levels with prematurity and its adverse effects on both mother and the foetus.

It was observed that vitamin D deficiency was very high in both preterm and term group. In the present study the overall prevalence of inadequate vitamin D level as high as 90%.

Overall low vitamin D level was seen more in the group of women who delivered preterm than the group of

women who delivered at term but this difference was not statistically. Similar finding was reported in the study conducted by Nalina Bhupornvivat et al and reported that the serum 25-OHD concentrations, the prevalence of vitamin D deficiency and insufficiency were not different between the preterm labor and the control groups.⁶

Most of the patients in preterm group and term group belonged to the age group of 18 – 25 years and in this age group vitamin D deficiency was most prevalent. J Zhou in their study in 2014 conducted in Southern China reported women who had normal vitamin D levels were significantly older at the time of delivery than the women with low vitamin D levels.⁷

In our study, it was found that in preterm group, 96.8% primigravida and 90.69% multigravida were vitamin D deficient. Pahuja et al in his study reported similar result.

In the present study, 64% women delivered in late preterm, 18.7% between 28-31⁺⁶ weeks of gestation and 17.3% between 32-33⁺⁶ weeks of gestation. 72.9% women who had late preterm birth were vitamin D deficient and 20.8% vitamin D insufficient. Similarly, vitamin D deficiency was significantly higher in the women who had early term delivery than late term. Study conducted by Sook Hyun Park et al in Korea in 2015, reported no significant difference in serum 25- (OH) D levels among early and late preterm.⁸

In our study, 23.5% delivered by caesarean section in preterm group and 27.3% in term group who were vitamin D deficient. Rate of caesarean section in vitamin D deficient women was higher in term group. But in case of vitamin D insufficient patients, rate of caesarean section was much higher in preterm group than term group. But vitamin D deficiency cannot be attributed for high rate of caesarean section as prematurity is in itself is a risk factor for higher caesarean section rate.

Dave A et al in 2017 reported in his study the association of vitamin D deficiency and caesarean deliveries. 23.5% pregnant women who delivered by caesarean section had vitamin D deficiency.⁹

In our study, NICU admission was more common in preterm group than in the term group. The most common cause of NICU admission was prematurity. 58.8% neonates born preterm and 22.7% neonates born term to vitamin D deficient mothers had NICU admission. Similarly, 63.25% neonates born preterm and 38.1% neonates born term to vitamin D insufficient mothers had NICU admissions. Our study shows that overall NICU admission was more in infant born to mother with low Vitamin D levels. Despite these findings it is difficult to conclude that the association of NICU admission in both the groups is solely related to vitamin D deficiency. Study conducted by Prasad et al reported 21.69% NICU admission in Vitamin D deficient group and 18.18% in Vitamin D sufficient group. They had higher number of NICU admission in vitamin D deficient group.¹⁰

Total 15 neonates in the preterm group and two neonate in the term group was diagnosed with neonatal sepsis and all of them (100%) were born to mother with inadequate Vitamin D level. It can be concluded that Vitamin D level may induce sepsis.

Conclusion

Present study does not show any association of vitamin D insufficiency and deficiency with preterm labour. No association of low vitamin D level and antenatal, intranatal or post-natal complications could be established. Neonatal sepsis was found to be more in the neonates born to the mother with low vitamin d level.

There is a need of large multi centric study with large sample size to conclude the association of vitamin D deficiency in preterm labour.

Cut-off value for vitamin D insufficiency of less than 30ng/ml and deficiency of less than 20ng/ml, may be high for Indian population as most of the population have low levels despite having no adverse effect in pregnancy and neonatal outcome. There is a need to reduce the cut off for vitamin D at which we label a patient as vitamin D deficient in Indian population.

Our study was that it is a prospective case control study and it included ethnically homogenous group living in the same environment and thus providing more valuable data to investigate.

Limitation

This study was done with small sample size and included women population attending our institute only and hence a large randomized controlled trial is necessary to determine the vitamin D levels in pregnancy and to draw guidelines regarding screening and supplementation.

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