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Research Article

Role of vitamin D in reducing the risk of preterm labour

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ABSTRACT

Background: Although vitamin D insufficiency is increasingly recognized as a health problem across the world, inadequate vitamin D status appears to be particularly prevalent in certain populations such as the elderly and pregnant women. With respect to the latter, impaired vitamin D status during gestation is associated with adverse outcomes in pregnancy such as preterm birth and poor neonatal outcome.

Methods: A total of 100 healthy, pregnant women in Sawangi, Meghe, Wardha, were recruited in 2012. Of these, 50 were randomised to receive either 2000 IU (study group) of vitamin D3 per day from 12-16 weeks of gestation of pregnancy. The remaining 50 pregnant women, who formed the control group were not supplemented with any drug. 25-hydroxyvitamin D [25(OH)D] in maternal blood was measured by chemiluminescence immunoassay, at recruitment and at the time of delivery and a serum 25(OH)D level <30 nmol/l was defined as deficiency.

Results: Patients had deficiency of vitamin D at baseline (80.00%) was converted into sufficient level (76.00%) in cases after vitamin D supplementation. It was statistically significant at 5% level as P value <0.05 and there was also evidence in reduction of preterm birth.

Conclusions: Maternal vitamin D deficiency is associated with significant increase risk for premature birth with P = 0.001. Maternal serum vitamin D sufficiency can be achieved by supplementing pregnant women with 2000 IU vitamin D supplements.

Keywords: Vitamin D, Preterm labour neonatal and maternal outcome

INTRODUCTION

Vitamin D was classified as a vitamin in the early 20th century and in the second half of the 20th century as a prohormone ("conditional" vitamin). It is a unique nutrient because it can be synthesized endogenously (skin) and it functions as a hormone. Impaired vitamin D status during gestation is associated with adverse outcomes in pregnancy such as preterm birth and poor neonatal outcome.

Preterm birth is, worldwide, the most challenging problem in obstetrics, but the prevention of prematurity has been difficult and ineffective because of its

multifactorial and partly still unknown aetiology.¹ However, infections alone may be associated with up to 40% of spontaneous preterm births, especially those taking place at an early gestational age.² During the past two decades, the association between maternal genital tract infections and ascending infection in the choriodecidual interface leading to preterm birth has been of special interest.³

Maintenance of normal pregnancy requires an effective coordination of anti-inflammatory and antimicrobial responses within the fetoplacental unit. Vitamin D plays a significant role in modulating both these processes

thereby helping in maintaining a healthy term pregnancy.⁴

So as to improve the outcome of these very preterm neonates, the current study intends to expand our knowledge of vitamin D and its effect in reducing the risk preterm labour.

In normal pregnancy, maternal 1,25-(OH)₂D increases progressively from the first trimester, to a peak of twice the non-pregnancy level in the third trimester. Pregnancy does not alter the clearance of 1,25-(OH)₂D. The increase in maternal serum level is due to increased production as well as to an increase in vitamin D binding protein.⁵ The increased production is primarily due to elevated 1α-hydroxylase activity in the maternal kidney, foetal kidney, placenta and decidua. The human endometrial decidua makes 1,25(OH)₂D and 24,25(OH)₂D and the placenta synthesizes 24,25(OH)₂D.⁶ Notably, the 24,25(OH)₂D synthesized by the placenta accumulates in bone and may be involved in ossification of the foetal skeleton. 1,25(OH)₂D also aids in the transformation of endometrial cells into decidual cells.⁷

Foetal calcium levels are higher than maternal throughout gestation. There is active transport of calcium across the placenta. Foetal vitamin D concentrations are up to 20% lower than maternal as measured in cord blood.⁸ Thus vitamin D deficiency is vertically transmitted.

Definition & prevalence of vitamin D deficiency

Vitamin D

Serum concentration of 25(OH)D is the best indicator of vitamin D status. In contrast to 25(OH)D, circulating 1,25(OH)₂D is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate. Levels of 1,25(OH)₂D do not typically decrease until vitamin D deficiency is severe.^{9,10}

Table 1: As per institute of medicine classification (2010).¹¹

Classification		
Deficiency	<30.0 nmol/l	<12 ng/ml
Inadequacy	30-49.99 nmol/l	12-20 ng/ml
Sufficient	50-74.99 nmol/l	20-50 ng/ml
Sufficient (with no increase benefit)	75-125 nmol/l	
Toxicity	>125 nmol/l	>50 ng/ml

*Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/ml). **1 nmol/L = 0.4 ng/ml

In the present study IOM 2010 recommendations are taken for classification of vitamin D deficiency.

Vitamin D deficiency and spontaneous preterm birth

Preterm labour is defined by the world health organization as the onset of labour prior to the completion of 37 weeks of gestation, in a pregnancy beyond 20 weeks of gestation.¹²

The incidence of preterm labour is 5-10% of all pregnancies. Incidence of preterm labour is 23.3% and of preterm delivery 10-69% in India. WHO 2010 shows India has the highest number of preterm birth i.e. 3519100.¹²

Table 2: Role of cytokines in initiation of preterm labour.

Cytokines	Action	Effect
IL-6, IL-8, IL-1, TNF-α	Degradation of collagen fibres	Cervical ripening
IL-1, TNF-α	Induce matrix metalloproteinases	Membrane rupture
IL-1, IL-2, IL-6, TNF-α	Increase PGE2, PGF2α	Uterine contractions

Infection

As many as 50% of spontaneous preterm births may be associated with infection.¹³ A variety of organisms, produce proteases which may reduce the strength of the chorioamniotic membrane. In addition they also produce phospholipase A2 in high concentrations. Phospholipase A2 is a precursor of prostaglandins which may play a part in the initiation of uterine activity. Normal genital tract flora are dominated by lactobacillus species., which produce lactic acid keeping the vaginal pH below 4.5 so discouraging the growth of other organisms. During pregnancy, the concentration of lactobacillus species increases 10 fold as pregnancy progresses. Anaerobic organisms become less common, aerobic organisms remain relatively constant which serves to protect the foetus at birth. As pregnancy progresses, increased levels of lactobacilli make the vaginal ecosystem inhibitory to the growth of many pathogenic or potentially pathogenic organisms.

Subclinical intrauterine infection has been implicated as a major etiologic factor in the pathogenesis and subsequent maternal and neonatal morbidity.¹⁴

Vitamin D and infections

the production of active vitamin D, the active vitamin D binds to VDR and vitamin D responsive elements unlocking DNA, targeting the genes that encode antimicrobial peptides. Vitamin D acts a potent stimulator of antimicrobial peptides particularly cathelicidin in the human body. It induces expression of cathelicidin in urogenital epithelial cells, and most importantly the monocyte macrophage system.

Apart from its antimicrobial properties, cathelicidin also has other immunoregulatory properties.

Vitamin D mediated intracrine induction of cathelicidin also occurs in decidual and trophoblastic cells of the placenta. Abundance of VDR in decidual and trophoblastic cells is consistent with localized responses to endogenous vitamin D. The placenta forms a natural barrier to foetal infections during pregnancy and both its maternal and foetal tissue is known to express antimicrobial proteins. A pivotal function of vitamin D production in the placenta might be to support the relatively high basal expression of antimicrobial proteins to combat infections by pathogens such as *Listeria* and group B *Streptococci* which are known to have a role in adverse events associated with pregnancy such as preterm labour.

Beside its role in production of cathelicidin, vitamin D also persuades hydrogen peroxide production and its secretion in human monocytes, activated by vitamin D there is an increased oxidative burst which helps in intracellular killing of organism.¹⁵

Since vitamin D has immunomodulatory and anti-inflammatory effects, such as the regulation of production and function of cytokines and neutrophil degranulation products that is important and relevant to prevent microbial invasion one may expect a protective effect on SPB risk.¹⁶⁻¹⁸ The various cells of the immune system express VDRs and are modulated by vitamin D.¹³ Although vitamin D action dampens the activation of the acquired immune system in response to autoimmunity, this hormone has key actions that enhance the innate immune system. It is involved in cell-mediated immunity by reducing the production of inflammatory cytokines such as IL-1, 6 and TNF that are involved in SPB.¹⁹⁻²¹ Human decidual cells are able to synthesize active 1,25 (OH)₂D₃. Therefore several studies point to the fact that vitamin D is involved in the regulation of acquired and innate immune responses at the foetal-maternal interface across gestation²² Vitamin D reduces the risk of SPB also by helping to maintain myometrial quiescence. Myometrial contractility is dependent on calcium release within the muscle cell and this process is regulated by vitamin D.²³⁻²⁵

Poor maternal vitamin D status might also increase risk of caesarean delivery by reducing strength of the pelvic musculature and the mother's ability to push and deliver vaginally leading a reduced ability to push and to a longer and more difficult labour.²⁶

Mothers with suboptimal vitamin D status have offspring with reduced intrauterine and postnatal skeletal development. Vitamin D supplementation has been found to effective in improving neonatal weight and APGAR score as well.

METHODS

This Longitudinal case control study was conducted in the department of obstetrics and gynecology at Acharya Vinobha Bhawe rural hospital Sawangi (Meghe), Wardha, during October 2012- September 2014.

Ethical clearance was taken from ethical committee of Jawaharlal Nehru medical college Sawangi (Meghe), Wardha.

All consecutively primigravida attending antenatal clinic at 12-16 weeks of gestation with uncomplicated pregnancy at Acharya Vinobha Bhawe rural hospital Sawangi (Meghe) were recruited.

Gestational age of the subjects was determined with best obstetric estimate using definitive menstrual history and ultrasonography done in first trimester.

Inclusion criteria

1. Primigravida
2. Singleton pregnancy
3. Gestational age: 12-16 weeks

Exclusion criteria

1. Gestational age less than 12 weeks and beyond 16 weeks.
2. Any clinical evidence of medical and metabolic disorder in pregnancy including maternal diabetes, chronic renal disease, hyperparathyroidism, collagen disease, gastrointestinal disease, lung disease, active thyroid disease, chronic hypertension.
3. History of any drug interfering with vitamin D metabolism like anticonvulsants, corticosteroids, thiazides, thyroxin, heparin, calcium channel blockers.
4. History of smoking and alcohol intake.

All patients selected for the study were explained about the methodology and relevance of the study. Written informed consent was taken.

Methodology of recruitment

All consecutive primigravida who attended the antenatal clinic at 12-16 weeks were screened. Subjects were evaluated on the basis of predesigned and pretested proforma with respect to history and clinical examination and investigation.

Enrolment was evenly distributed throughout the year to ensure vitamin D status.

Serum vitamin D concentration of subjects were done at their first prenatal visit and then at the time of their delivery.

Subjects were followed up with monthly study visits, which continued until delivery which included the routine investigation.

Outcome of labour: at the time of delivery following details were noted

- 1) Mode of delivery-preterm delivery/full term normal delivery/caesarean section
- 2) If caesarean delivery, then indication
- 3) Birth weight & APGAR score

Intervention

Pregnant women who were recruited in study group were supplemented with vitamin D 3 2000 IU irrespective of gestational age (12-16 weeks) at recruitment till term.

Adherence to prescribed vitamin D supplementation regimen was measured by maternal self-report and pill count at each follow up visit. If a woman had missed two or more visits or she fails to take 50% of the prescribed medication, she was exited from the group.

Source of vitamin D

Vitamin D3 tablets trade name Justdee manufactured by Stedman pharmaceuticals were used with Vitamin D3 of 2000 IU.

Dosage

One gram is 40000000 (40×10^6) IU, equivalently 1 IU is 0.025 μg 2000 IU = 50 μg .

Vitamin D levels

5 ml of fasting sample was collected after recruitment. And patients of study group were supplemented with vitamin D3 and at delivery fasting sample was collected for both groups. Blood sample was centrifuged at 3000rpm and serum was stored at -20°C and tested for vitamin D levels.

Mean serum 25(OH)D levels were measured by Roche diagnostic ELECSYS (Electrochemiluminescence immunoassay) 2010 Cobase E 411 Analyser Immunoassay System Germany. The minimal detectable limit of the 25(OH)D assays is 3 ng/mL.

Statistical analysis

Statistical analysis was performed using chi square test and student t-test at 95% confidence interval. Software used for the analysis is SPSS 17.0 version and Graphism 4. Results were tested at 5% level of significance.

RESULTS

In the present study mean age was found 23.94 ± 3.11 years in control group whereas in study group it was 25.02 ± 2.63 years which was not comparable.

Mean gestational age in cases was 14.54 ± 1.35 in weeks whereas in the control it was 15.68 ± 1.57 in weeks.

74% of pregnant women were found vitamin D deficient (<30 nmol/l) in both study group and control group, 12% were having inadequate vitamin D levels (30-49.99 nmol/l) and only 14% were having vitamin D sufficiency (50-74.99 nmol/l).

Maximum patients had deficiency of vitamin D at baseline (80.00%) was converted into sufficient level (76.00%) in cases after vitamin D supplementation. It was statistically significant at 5% level as P value <0.05 .

Statistically non significance difference was found in control in baseline serum vitamin D level and at delivery of patients without vitamin D supplementation. The mean gestational age in control group was 35.98 ± 3.57 in weeks whereas in the cases it was 38.10 ± 2.35 in weeks which was comparable as $P <0.05$.

40 women (80.00%) in cases delivered full term vaginal delivery which was significantly more than that in control group, in which only 16 women (32.00%) delivered full term. It was found that 8.00% women had delivered preterm vaginally in cases as compared to 38.00% in control group which was statistically significant ($P = 0.001$). Lower segment cesarean section was also more in control 15 (30%) as compare to cases (12%). Mean weight of baby was significantly low in control group 2.33 ± 0.52 in kg compared to that in cases it was 3.16 ± 0.58 in kg as $P <0.05$.

Table 3: Effect of vitamin D supplementation among pregnant women.

	Cases	Control
Age	23.94 ± 1.45	25.02 ± 1.23
Gestational age at recruitment (Mean)	14.54 ± 1.24	15.68 ± 1.23
Gestational age at delivery (Mean)	38.10 ± 2.35	35.10 ± 1.23
Vitamin D levels at recruitment (nmol/L)	3.69 ± 10.57	9.45 ± 11.65
Vitamin D levels at delivery (nmol/L)	29.85 ± 9.85	25.46 ± 3.69
Preterm birth	6 (12.00%)	15 (30.00%)
Caesarean section	4 (8.00%)	19 (38.00%)
Apgar score		
1 Min	8.38 ± 1.23	7.10 ± 0.73
5 Min	9.44 ± 1.10	8.58 ± 1.75
Birth weight	3.16 ± 0.58	2.33 ± 0.52

Mean APGAR score at 1 minute was significantly low in control group was 7.10 ± 0.73 compared to that in cases was 8.38 ± 1.67 which was comparable. This was statistically significant as $P < 0.05$. Mean Apgar score at 5 minute in control group was 8.58 ± 1.75 whereas in cases it was 9.44 ± 1.07 which was comparable. This was statistically significant as $P < 0.05$.

DISCUSSION

The data on vitamin D supplementation during pregnancy is limited. This study represents the first Indian study on role of vitamin D in reducing the risk of preterm birth.

In the present study mean age among pregnant women was 23.94 ± 3.11 years in control group whereas in study group it was 25.02 ± 2.63 years. It was found that maximum (67%) participants were of lower middle economic status according to modified Kuppaswamy classification. In present study the mean gestational age in cases was 14.54 ± 1.35 in weeks whereas in the control it was 15.68 ± 1.57 in weeks

A high prevalence of hypovitaminosis D was found among both groups. In present study 74% of women among study and control group were having vitamin d deficiency i.e. serum 25(OH) vitamin D levels < 30 nmol/l, 12% were found to have inadequate vitamin D levels (> 30 but < 50 nmol/l) and 14 % were having vitamin D sufficiency ($50-74.99$ nmol/l).

The first Indian study on vitamin D status in singleton pregnancy by Goswami²⁶ et al. in year 2000 reported 60-70% prevalence of vitamin D deficiency. Subsequently Sachan²⁷ et al in 2005 also reported 84% prevalence of vitamin D deficiency in women with singleton pregnancies. Other Indian studies have reported similar findings in singleton pregnancies.

Vitamin D supplementation can improve vitamin D status during pregnancy. In present study significant (P value < 0.05) improvement in vitamin D levels at delivery were seen in women who were supplemented with 2000 IU vitamin D/day. 76% of pregnant women who were supplemented with 2000 IU vitamin D/day from 12-16 weeks till delivery achieved sufficient vitamin D levels (> 50 nmol/l).

Bruce et al. (2011)²⁸ found similar results in significant ($P < 0.0001$) improvement in vitamin D status at delivery in pregnant women with 2000 IU vitamin D supplementation/day. He found that 70.6% of women achieved sufficient vitamin D levels with 2000 IU/day vitamin D supplementation. In their study pregnant women were supplemented with 4000 I.U as well but there was no significant difference among both group however sufficiency was achieved better in 4000 IU.

Vitamin D deficiency increases the risk for preterm birth. In present study significant ($P = 0.001$) increase number of preterm birth were found among control group who

were vitamin D deficient with mean vitamin D levels < 50 nmol/l as compare to study group who were supplemented with vitamin D and had sufficient vitamin D with mean vitamin D levels > 50 nmol/l. As compare to present study Shibata M et al. (2011)²⁹ also found high prevalence hypovitaminosis D in pregnant Japanese women with serum concentration of vitamin significantly low in women with preterm labour (11.2 ± 3.2 ng/ml) in comparison with term controls, (15.6 ± 5.1 ng/ml).

In present study the mean gestational age in pregnant women with 2000 IU vitamin D supplementation per day was significantly ($P < 0.05$) improved 38.10 ± 2.35 weeks as compare to control group 35.98 ± 3.57 weeks. Preterm birth in cases was significantly low (8%) ($P = 0.001$) in which sufficient vitamin D (> 50 nmol/l) levels were achieved by supplementing 2000 IU vitamin D/day. Our results were found similar to other studies in related to vitamin D supplementation and reducing the risk for preterm birth.

Wagner C et al. 2012³⁰ studied the effectiveness of vitamin D supplementation in reducing preterm birth risk in 494 pregnant women at medical university of South Carolina Charleston and observed similar results with inverse relation between vitamin D supplementation and preterm birth. Preterm labour/birth was inversely associated with initial ($P = 0.001$) and month prior to delivery 25(OH)D ($P = 0.008$).

Bruce H et al. (2011)³¹ also studied that vitamin D sufficiency may protect against preterm birth from preliminary analysis of a large cohort of pregnant women supplemented with vitamin D in South Carolina and their initial findings show that the risk of preterm birth at 37 and 32 weeks was reduced among women taking vitamin D. They also reported mean gestational age at delivery among women with 2000 IU vitamin D supplementation was 38.8 ± 1.8 weeks.

Mehrdad Shakiba et al. Yazd, Iran (2009)³² a total of 51 healthy, pregnant women in, were recruited and supplemented vitamin D and results were a low rate of prematurity among neonates born to women who have been supplemented with vitamin D. Among the 51 women who received vitamin D-supplementation, only 1 (2%) neonate was delivered prematurely [95% Confidence Interval (CI) 1.3-5.5].

In present study it was also found that rate of caesarean section was also more in control 15 (30%) as compare to cases in study group 6 (12%). Similarly Henan D et al. (2014)³³ studied, the correlation between vitamin D level and primary caesarean section. They found 46% ($n=23$) of them delivered by caesarean section there was an inverse association with having a caesarean section and serum 25(OH)D levels. Theresa et al. (2011)³⁴ also examined a cohort of 1153 pregnant women found out that there is significant increase risk for primary caesarean section for women of deficient vitamin D levels [25(OH)D < 30 nmol/l].

In the present study risk for caesarean for prolonged labour was increased in control group 8 (38.10%) with [25(OH)D <30 nmol/l] as compared to study group i.e. 1 (4.76%) women.

Theresa et al (2011)³⁴ also found women with a primary caesarean and 25(OH)D was <30 nmol/l there was a 2-fold increase in caesarean for prolonged labour, no increase in risk was found when levels fell between 30 and 49.9 nmol/l.

Merewood et al. (2007),³⁵ enrolled 253 women found that 28% of women with serum 25(OH)D <37.5 nmol/l had a primary caesarean section, compared to only 14% of women with 25(OH)D >37.5 nmol/l (P = 0.012).

Vitamin D supplementation of pregnant mother is associated with increased skeletal growth and bone mass in offsprings. In present study significant improvement in mean birth weight (3.16 ± 0.58 in kg) of babies was found in women with vitamin D supplementation as compare to control group (2.33 ± 0.52 in kg) as P <0.05. There was also significant improvement in Apgar score at birth of new-borns with mothers having adequate intake of vitamin D. Both one minute and five minute were significantly higher 8.38 ± 1.67 and 9.44 ± 1.07 respectively.

Brooke et al. (1980)³⁶ first reported reduced incidence of low birth weight babies in vitamin D supplemented Asian mothers. In treatment group mean birth weight was 3157 grams which was significantly higher than control group with P <0.05.

Marya et al. (1988)³⁷ also reported higher body weight, in offsprings of mothers who received vitamin D during pregnancy to those who did not receive vitamin D. APGAR score at birth was higher in new-borns of mothers with adequate vitamin D intake than in new-borns whose mothers had inadequate intake.

In Pakistan Ramzan S et al. (2014)³⁸ conducted open label randomized controlled trial of antenatal vitamin D supplementation in 193 pregnant women and observed One and five minute APGAR scores were significantly higher: one minute (7.10 ± 0.66 vs. 6.90 ± 0.50, P = 0.026); and five minute (8.53 ± 0.68 vs. 8.33 ± 0.81, P = 0.051) respectively among those with vitamin D supplementation.

Vitamin D supplementation and effect on birth weight and APGAR score:

There was no adverse effect noted among pregnant women with vitamin D supplementation.

There was no evidence any maternal and neonatal mortality in present study.

This study has certain limitation.

- Only 100 pregnant women fulfilled the inclusion criteria were included in the study, larger number of randomized control trial is needed to give conclusive outcome.
- Owing to the safety concerns in use of 2000 IU of vitamin D supplementation during pregnancy, the study was designed to begin supplementation starting at twelfth week of gestation, beyond the period of early organogenesis. Additional studies will be necessary to ascertain safety of vitamin D supplementation before twelfth week of gestation

CONCLUSIONS

- There is high prevalence of vitamin D deficiency in pregnant women to an extent of 74%.
- Maternal vitamin D deficiency is associated with significant increase risk for premature birth with P = 0.001.
- Maternal serum vitamin D sufficiency can be achieved by supplementing pregnant women with 2000 IU vitamin D supplements.
- Vitamin D sufficiency significantly reduces the risk for preterm birth as compared to pregnant women with vitamin D deficiency.
- Vitamin D supplementation is also associated with increase in birth weight of baby and improving the Apgar score at birth.
- There is increased risk for caesarean section in pregnant women with vitamin D deficiency.
- This improvement in vitamin D status was achieved without evidence hypervitaminosis D or an increase in adverse events during pregnancy.
- There was no evidence of maternal and neonatal mortality during our study.

Vitamin D deficiency and insufficiency is problem that has been highlighted in literature for a number of years but response is slow. Vitamin D supplementation can be a safe and cheap method of improving the nutritional status of pregnant women and achieving good maternal and foetal outcome in terms of prematurity and other comorbidities.

Thus vitamin D supplementation may be considered as a method of primordial prevention in improving the vitamin D status in adolescent girls and women in reproductive age group so as to reduce maternal and perinatal morbidity.

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