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Effects of Maternal Vitamin D Levels on Mother and Health of Newborn

Dr Ridhum Tuli[1], Dr Robin Tuli[2]

Tuli Diagnostic Centre, Amritsar. Punjab. India

Abstract: ***This study is evaluates 25-hydroxy (OH) vitamin D levels of pregnant women and the effects of maternal vitamin D deficiency on her pregnancy and neonates. Optimal levels of vitamin D are essential as early as from the beginning of pregnancy for the risk reduction of pre-eclampsia and other pregnancy complications like gestational diabetes mellitus, pre-term labor and neonatal hypocalcemia.***

Keyword: 25 hydroxy (OH) vitamin D, maternal vitamin D, Gestations hypertension (GHT), Pre-eclampsia, neonatal hypocalcemia, gestational diabetes mellitus (GDM)

1. Introduction

Vitamin D is a fat-soluble vitamin. It is photochemically synthesized through skin in individuals receiving even mild sunshine and do not need a dietary source. It is essential for maintaining healthy bones and teeth. It also plays many other important roles in the body, including muscular movement, neurological signal transmission, regulating inflammation and immune function.

Despite its name, vitamin D is not a vitamin but a hormone or a pro-hormone. Vitamin D deficiency is the most common metabolic bone disease in the world and is easily treatable as well as preventable with sun exposure and dietary supplementation [1].

Although the body can create vitamin D, but some people are more likely to be at risk of a deficiency than others. Factors that can influence vitamin D levels in our body include:

- Skin color: Pigmentation in the skin reduces the body's ability to absorb ultraviolet B (UVB) rays from the sun.
- Lack of sun exposure: People who live in northern latitudes or areas of high pollution, work night shifts, or are homebound.
- Breastfed infants.
- Older adults: The skin's ability to synthesize vitamin D with age. Older adults may also spend more time indoors.
- Those with conditions that limit fat absorption: Vitamin D is fat-soluble, meaning intake is dependent on the gut absorbing dietary fats. Conditions that limit fat absorption can decrease vitamin D intake from the diet.
- People with obesity: High levels of body fat can limit the body's ability to absorb vitamin D from the skin.
- People following a gastric bypass: This surgery bypasses a part of the upper intestine that absorbs large amounts of vitamin D. This bypass can cause a deficiency.

Maternal vitamin D insufficiency during pregnancy is a common issue and a significant public health problem at the global level. The fetus depends on the maternal supply of vitamin D, calcium and phosphorus, which is transmitted across the placenta [3].

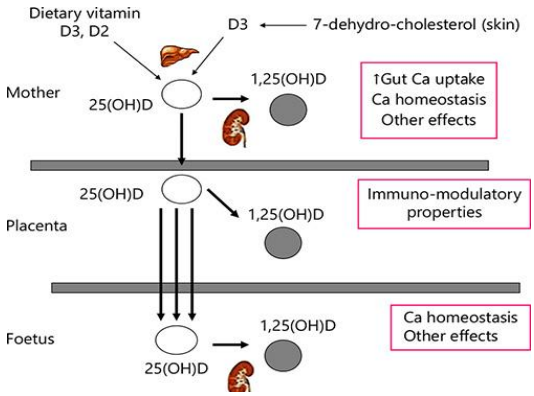


Figure 1: Materno-fetal vitamin D transfer. Courtsey [3]

2. Materials and Method

30 antenatal female subjects were included in present study.

Thyroid stimulating hormone (TSH), calcium, glucose, phosphorus and 25-hydroxy (OH) vitamin D estimation through blood samples were performed on these subjects during their ante-natal visit and were then followed up till the time of delivering their infant. Neonatal calcium and 25-hydroxy vitamin D were also estimated for the neonates. Each subject was asked about lifestyle questionnaire and this included details regarding the ethnic group, maternal age, parity, height, weight, tobacco/cigarette smoking, alcohol consumption (in units per week) or any use of recreational drugs. We also documented the estimated hours of daily sun exposure, use of vitamins, diet (vegetarian or vegan) and clinical features suggestive of vitamin D deficiency.

Definitions/ terminology adopted during this study:

- Pre-eclampsia toxemia (PET)/ Gestational hypertension (GHT): This is a complication of pregnancy in which pregnant female develops high blood pressure/ hypertension, with or without proteinuria.
- Eclampsia: A condition in which one or more convulsions occur in a pregnant woman suffering from hypertension.
- Severe Morbidity in ante-natal women: The cases included in this category morbid ante-natal women needing intensive care due to any condition like

eclampsia, renal failure, HELLP (Hemolysis, Elevated liver enzymes and Low Platelets) syndrome, mother's hospital stay more than 7 days or post-partum hemorrhage.

- Gestational Diabetes mellitus (GDM): is defined as glucose intolerance resulting in hyperglycemia of variable severity with onset during pregnancy. GDM is caused due to a hormone released by placenta that keeps the body from using the insulin as it should.
- Neonatal hypocalcemia: is defined as low levels of calcium in a new born. Serum ionized calcium less than 1mmol/L in a full-term infant and less than 0.75 mmol/L in a pre-term infant.

Exclusion Criteria:

Women with pre-existing history of diabetes, hypertension, sarcoidosis, osteomalacia, renal dysfunction and tuberculosis were excluded from the study.

3. Observations

Association of vitamin D status in development of Pre-eclampsia/gestational hypertension and Severe morbidity in ante-natal women.

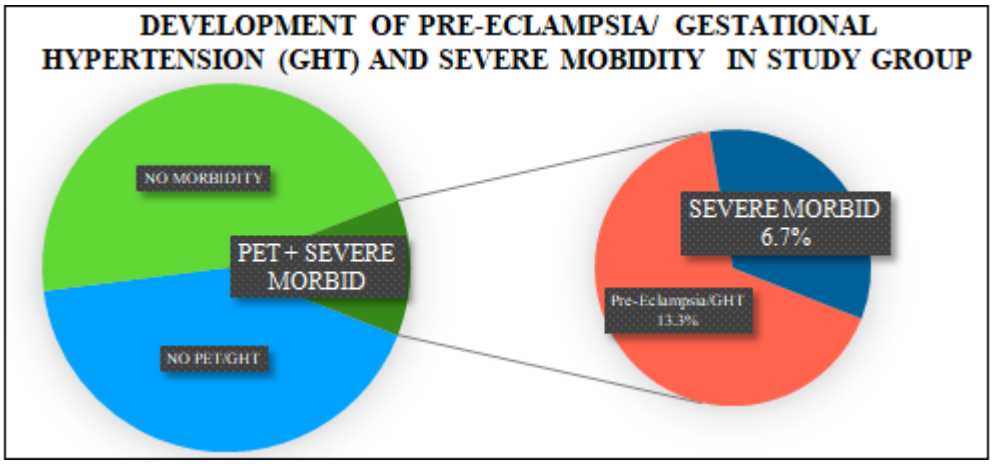
In the present study, 86.7% & 93.4% women did not develop GHT and severe morbidity respectively. No case with GHT/PET and severe morbidity were diagnosed with adequate vitamin D in mother.

High significance with p value <0.05 were obtained in development of PET/GHT and severe morbidity in ante-natal women with deficient vitamin D. p-value obtained for cases having PET/GHT is 0.001 and for woman developing severe morbidity is 0.03.

Table 1: Effect of vitamin D in development of Pre-eclampsia toxemia (PET) / Gestational hypertension (GHT) and Severe morbidityin ante-natal period.

	Vitamin D Status in ante-natal woman			Vitamin D Status in ante-natal woman	
	Deficient	Adequate		Deficient	Adequate
No PET/GHT	5 (16.7%)	21 (70%)	No morbidity	5 (16.7%)	23 (76.7%)
Development of PET/GHT	4 (13.3%)	Nil	Severe morbidity	2 (6.7%)	Nil
Total Cases: 30					

1. PETcases, Chi-square (χ^2) value obtained is 10.769 having p-value of 0.001, d=0.192, 95% CI (0.087, 0.423)
2. Severe morbidity cases, Chi-square (χ^2) is 5.0 having p-value 0.03, d=0.25, 95% CI (0.132, 0.475).



This is graphical presentation depicting, 20% cases with PET/GHT and in severe morbidity were obtained. 13.3% cases were diagnosed with Pre-eclampsia toxemia/ Gestational hypertension and 6.7% cases were categorized under severe morbidity. All these cases were found to have deficient maternal 25 (OH) vitamin D.

Association of vitamin D status in development of Gestational Diabetes mellitus (GDM)

Development of Gestational diabetes mellitus (GDM) in this study was not found to have influence of vitamin D deficiency on the subjects in ante-natal period. However, 16.7% of the subjects in this study developed GDM in their ante-natal period. This could be because of age or other environmental factors but was beyond the scope of the present study.

Table 2: Association of vitamin D in development of Gestational Diabetes Mellitus (GDM) in ante-natal period

	Vitamin D Status of Ante-natal woman		Total Number of Cases
	Deficient	Adequate	
No Gestational Diabetes	6 (20%)	19 (63.3%)	25 (83.3%)
Development of Gestational Diabetes	3 (10%)	2 (6.7%)	5 (16.7%)
Total Cases			30

Chi-square χ^2 value obtained is 2.571 having p-value of 0.11 (not significant).

Association of vitamin D status in deliveries done through caesarian section.

We observed two times more caesarian section in women with vitamin D deficiency than in women with adequate 25 (OH) vitamin D in our study. A significant p-value of 0.004

is obtained indicating effect of vitamin D on normal vaginal delivery.

Table 3: Effect of vitamin D on labor and delivery through Caesarian section.

	Vitamin D Status of ante-natal woman		Total Number of Cases
	Deficient Vitamin D	Adequate Vitamin D	
Normal Vaginal delivery	3 (10%)	18 (60%)	21 (70%)
Delivery through Caesarian Section	6 (20%)	3 (10%)	9 (30%)
Total Cases			30

Chi-square χ^2 value obtained is 8.231 having p-value of 0.004.
ODDs Ratio: d= 0.83 95% Confidence interval (0.013, 0.529)

Association of vitamin D status in ante-natal woman & pre-term deliveries

Although 16.7% women with deficient vitamin D delivered at full gestation period compared to 13.3% pre-term deliveries with deficient vitamin D. The p-value obtained is 0.008 showing high significance and impact on gestational period of ante-natal women causing more pre-term deliveries when compared with 83.3% of full-term deliveries having adequate vitamin D levels in ante-natal mothers.

Table 4: Effect of maternal vitamin D status on gestation and pre-term deliveries

	Vitamin D Status of Ante-natal woman		Total Number of Cases
	Deficient vitamin D	Adequate vitamin D	
Full gestational term delivery	5 (16.7%)	20 (66.7%)	25 (83.3%)
Preterm labor and delivery	4 (13.3%)	1 (3.3%)	5 (16.7%)
Total Cases			30

Chi-square χ^2 value obtained is 7.143 having p-value of 0.008.
ODDs Ratio: d= 0.063 95% Confidence interval (0.006, 0.689

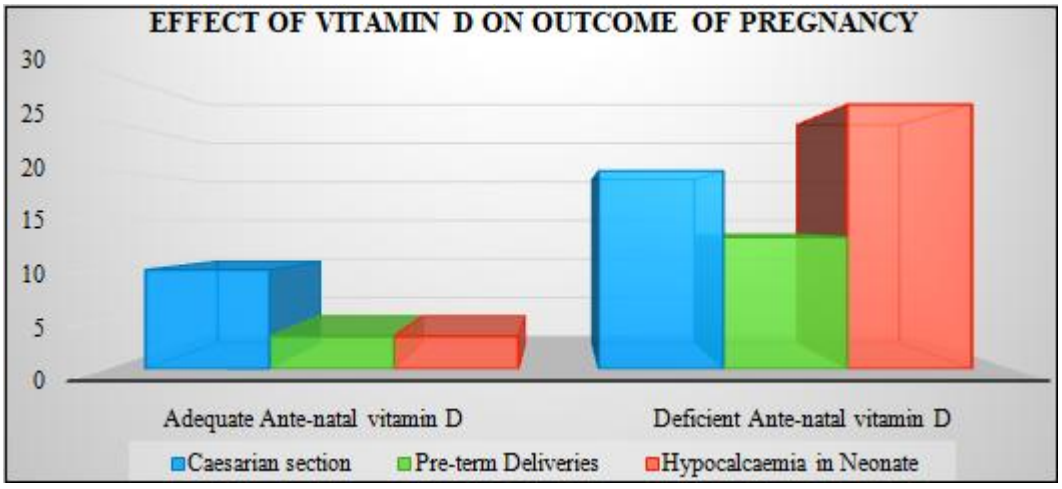
Association of vitamin D status of mother on her new born

Neonates born to vitamin D deficient mothers were 8 times at more risk of development of hypocalcemia as compared to only 3.3% of neonates developing hypocalcemia at birth in babies born to mothers with adequate vitamin D levels.

Table 5: Effect of maternal levels of vitamin D on neonates

	Vitamin D Status of Mother		Total Number of Cases
	Deficient	Adequate	
Normal Neonate Calcium	1 (3.3%)	20 (66.7%)	21 (70%)
Reduced Neonate Calcium (Hypocalcemia)	8 (26.7%)	1 (3.3%)	9 (30%)
Total Cases			30

Chi-square χ^2 value obtained is 21.232 having p-value of <0.00001.
Odds Ratio: d= 0.006, 95% Confidence interval (0.0, 0.113).



This bar graph summarizes the influence of vitamin D status during ante-natal period and its effects on the outcome of the pregnancy. We observed 2 times more caesarian sections, 5 times increased chances of pre-term labor and manifold risk of developing hypocalcemia in a neonate with mothers having deficient vitamin D levels.

4. Discussion

- In the present study, 70% women did not develop PET/ Gestational hypertension having adequate vitamin D. 6.7% females became severely morbid with deficient25 hydroxy vitamin D levels in our study. This was found to be concordant with a sub-study of a randomized control trial of vitamin D supplementation in pregnancy that supplementation reduced risk of pre-eclampsia and Vitamin D insufficiency could be associated with PET [4]. Maternal calcium status might be important in the etiology of PET, as calcium supplementation can reduce PET risk particularly in women with low calcium intake [5]. Aghajafari et al reported in another meta-analysis of vitamin D deficiency and pregnancy outcomes, and showed a significant association between PET and 25 (OH)D insufficiency [6]. Pre-eclampsia and vitamin D deficiency are directly and indirectly associated through biologic mechanisms including immune dysfunction,

placental implantation, abnormal angiogenesis, excessive inflammation, and hypertension [7].

- In the present study, 25 (OH) vitamin D deficiency did not show any significance in development of gestation diabetes mellitus. Hannah JW Farrat, showed no overall relationship between maternal 25 hydroxy (OH) vitamin D status and risk of GDM [8].
  However, a study done by Ji JL et al, suggests that vitamin D contributes to various factors associated with the propensity to develop impaired glucose tolerance, such as insulin sensitivity, beta cell function and insulin secretion. Immune dysfunction through inflammatory dysregulation (cytotoxic T-lymphocyte activation) links vitamin D deficiency with compromised maternal-fetal tolerance and increased risk of GDM [9].
- We observed increased cases of caesarian sections if maternal 25 (OH)D is deficient. Vitamin D deficiency may reduce pelvic muscle strength and control [10]. A study conducted by Merewood A. et al, assessed 25 (OH)D in early pregnancy or at delivery, reported an increased risk of Caesarean delivery in 25 (OH)D deficient women [11]. Pre-term labor or early deliveries before full term were found to be strongly associated in mothers with deficient 25 (OH) vitamin D in our study. Systemic inflammation, which is associated with a low 25 (OH) D status, may accompany the events leading to the initiation of preterm birth, including membrane rupture and uterine contractions [12]. De Regil et al found that women who received vitamin D supplements during pregnancy had a lower risk of having a preterm birth than those women receiving no intervention or placebo [7, 13].
- Hypocalcemia was very likely in the neonates born to 25 hydroxy (OH) D deficient mothers. During pregnancy, significant alterations to calcium and phosphate metabolism occur; allowing the accretion of calcium within the fetal skeleton, particularly during the third trimester vitamin D supplementation in pregnancy can increase umbilical cord venous and neonatal serum of pregnancy. Infants of mothers with vitamin D deficiency have reduced concentrations of 25 (OH) D in their cord blood samples [14]. Maternal vitamin D deficiency during pregnancy can also affect calcium homeostasis, causing hypocalcemia and craniotabes. Neonatal rickets is an uncommon consequence of vitamin D deficiency during pregnancy [2]. The fetus is dependent on the mother for accretion of approximately 30g of calcium to enable skeletal development and rickets has been reported in infants born to mothers with vitamin D deficiency. Clinically, neonatal hypocalcemia can result in seizures and has been associated with softening and thinning of the skull (craniotabes) [9]. Maternal vitamin D deficiency may represent an important risk factor for the development of rickets in children [15]. Vitamin D supplementation consistently reduced the incidence of symptomatic hypocalcemia in neonates [16]. The nutritional vitamin D status of the fetus and neonate is totally dependent on the vitamin D stores of the mother, thus, if the mother has hypovitaminosis D, her fetus will experience depleted vitamin D exposure throughout the developmental period [17]. Vitamin D supplementation of vitamin D deficient pregnant women prevents neonatal vitamin D deficiency [16, 18, 19]. The UK Department of Health currently recommends routine antenatal vitamin D supplementation with 400 IU cholecalciferol daily throughout pregnancy for all women, independent of ethnicity and other risk factors for vitamin D deficiency. There is good evidence to suggest that supplementation is important in reducing the risk of neonatal hypocalcemia and increasing neonatal 25 (OH) D status [20].
- Screening of vitamin D levels at the pre-conceptional period or at the first trimester should be recommended in pregnant women with high risk of vitamin D deficiency such as obese women, subjects with dark skin, hardly cover, under corticoid treatment, hypertension, pre-gestational diabetes mellitus, or autoimmune diseases so that they could receive appropriate treatment and monitored accordingly [3].
- Further increased risk is associated with dark-skinned individuals, lack of UV-B exposure, solely breastfed infants and prematurity. Despite recommendations for supplementation in all breast-fed infants and fortification of multiple household food items, it is still a relatively common nutritional deficiency. Proper childhood maintenance visits with growth and development screenings are critical for early detection of this easily treatable condition [1].
- Although there is modest evidence to support a relationship between maternal 25 (OH)D status and offspring birth weight, bone mass and serum calcium concentrations, these findings were limited by their observational nature (birth weight, bone mass) or risk of bias and low quality calcium concentrations [21].
- Antenatal vitamin D supplementation is now recommended for all pregnant women in many national guidelines as severe maternal vitamin D deficiency can result in symptomatic neonatal hypocalcemia, obstetric complications, offspring musculoskeletal development [20]. Further research is needed to determine the long-term consequences of maternal and neonatal vitamin D deficiency and the optimum timing and dosing of vitamin D in pregnancy [2, 22].

5. Conclusion

Pregnancy is a physiologically unique period, involving hemodilution, hormonal and metabolic changes. Supplementation with cholecalciferol increases maternal serum 25hydroxy (OH) vitamin D concentration. Optimal levels of vitamin D areessential as early as from the beginning of pregnancy for the risk reduction of pre-eclampsia, neonatal hypocalcemia and other pregnancy complications. All pregnant women may benefit from vitamin D supplementation in pregnancy and in the postpartum period.

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