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Association Between Maternal Vitamin D Status And Infantile Nutritional Rickets In A Hospital Setting: A Cross-Sectional Study

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ABSTRACT:

Objective: *This study aimed to evaluate the association between vitamin D status in breast-feeding mothers and the presence of rickets in their infants under one year of age.*

Methods: *A cross-sectional study was conducted with 100 mother-infant pairs divided into two groups: 50 pairs with rachitic infants and 50 with healthy infants. Serum Vitamin D, calcium (Ca), alkaline phosphatase (ALP), and phosphate (P) levels were measured in both groups. Statistical analyses, including t-tests and regression analyses, were used to examine relationships between maternal vitamin D levels and infant rickets.*

Results: *Mothers of rachitic infants had significantly lower serum vitamin D levels (mean = 18.5 ± 4.2 ng/mL) compared to mothers of healthy infants (mean = 32.7 ± 5.5 ng/mL, $p < 0.01$). Infants with rickets displayed elevated ALP and lower calcium levels compared to healthy infants. Regression analysis indicated a strong inverse correlation between maternal vitamin D levels/status and the incidence of infantile rickets ($p < 0.01$).*

Conclusion: *Maternal vitamin D deficiency (VDD) is significantly associated with infantile rickets, suggesting the importance of maternal supplementation of Vitamin D to prevent rickets in their breastfed infants.*

Introduction

The major source of circulating 25-hydroxyvitamin D concentration [25 (OH) D] in the young infant is the mother. Maternal vitamin D status is an important factor in determining the vitamin D status of the infant and their risk of developing VDD and infantile nutritional rickets. As a result of the research over the last 30 years, the role played by maternal vitamin D status during pregnancy and lactation in influencing the vitamin D status of the newborn and young infant has been increasingly realized[1].

Rickets is a bone disorder caused by low levels of vitamin D in the body[2]. Vitamin D is the essential precursor of 1,25-dihydroxyviramin D_3, the steroid hormone required for calcium absorption, bone development and growth in children. Vitamin D helps to control the levels of calcium and phosphate in the bones — the important minerals that give bones their strength. Low levels of vitamin D lead to a loss of calcium and phosphate from the bones, causing bones to grow softer and weaker over time. Serum levels of 25 (OH) D are a measure of the body's vitamin D stores and used for diagnosing VDD. In infants, stores of vitamin D reflect maternal stores, and human breast milk is a poor source of vitamin D[3-5].

The clinical picture of nutritional rickets was first described by Whistler (1645) and Glisson (1650)[6], who reported that the disease rarely occurred before 6 months of age and was most prevalent between 6 months and 2.5 years of age. Later studies[7-9] have shown that symptomatic VDD can develop early in infancy. The disease is now known to occur most likely during periods when children's bones grow rapidly, and is most often found in children 3 months to 18 months of age.

In the past few decades, the burden and prevalence of infantile nutritional rickets have been reported in studies from developing as well as developed countries. In most of the studies common factors that seem to be important include among others, maternal VDD & the infants being breastfed[1]. A high prevalence of maternal VDD has been demonstrated in studies examining the vitamin D status of mothers having rachitic children [3, 10]. Furthermore, a higher prevalence of maternal VDD has been found in the mothers of rachitic than non-rachitic children[11]. It was suggested by the authors in that study that the vitamin D status of mothers of children with VDD rickets should be determined [11]. A link between maternal VDD and infantile rickets can be found if the data from these studies are taken together. This link may be a joint effect of the positive relationship between maternal vitamin D nutritional status and vitamin D status in early infancy[11, 12] and a similar pattern of sun exposure of mother and child. At least in some regions, it is reasonable to view maternal VDD & rickets as inter-related, with important implications for a change in the strategy for comprehensive prevention of VDD in women and children[11].

Because human breast milk is such a poor source of vitamin D, breastfed infants are particularly vulnerable to VDD & hence constitute an important group to target for vitamin D supplementation. Over the past few decades, sporadic reports have noted persistent vitamin D deficiency rickets almost always in breast-fed infants. Maternal vitamin D supplementation (28000 IU/week) during the third trimester of pregnancy until six months postpartum reduced the risk of infantile biochemical rickets[13, 14].

Most of the previous reports have focused on infants & not their mothers. These reports and studies have put emphasis upon factors affecting the growth of infant after their birth, like non- supplementation of vitamin D during breast feeding, dark skin pigmentation, reduced sun exposure and certain dietary factors as the causes of rickets and VDD. Thus, although vitamin D metabolism is considered to be well understood, the importance of maternal vitamin D status directly influencing an infant's vitamin D levels through breast milk, appears to be poorly appreciated in clinical practice. Limited studies have investigated this relationship's impact on infant bone health, especially in hospital settings.

Aim of this study was to find association if any, between vitamin D statuses in breast-feeding mothers and the presence of nutritional rickets in their infants.

Materials and Methods

A cross-sectional comparative study was conducted at the departments of Pediatrics & Biochemistry, Medical Teaching Institution (MTI) QHAMC/NMC Nowshera, Khyber Pakhtunkhwa, Pakistan, from March 2024 to August 2024, after approval from the ethical committee of the institution. Non-probability convenience

sampling was used to randomly select a total of 100 mother-infant pairs, 50 rachitic and 50 healthy, age (approximate) & sex matched, infants (one month to one year of age) with otherwise their healthy breastfeeding mothers, visiting the pediatric department of the hospital for various ailments of their infants, during the study period. Infants exclusively breastfed, and born to mothers not on vitamin D supplements were included. While infants with congenital bone disorders, liver and kidney diseases or mothers with known metabolic bone diseases & other comorbidities were excluded.

After taking consent from the mothers and explaining them the purpose of study, the study subjects were enrolled. Demographic data and anthropometric indices of both infants & mothers were recorded on an already designed proforma/questionnaire. The subject mother- infant pairs of both rachitic & non-rachitic group were then sent to Biochemistry lab for the determination of study parameters.

Approximately 5–7 mL of blood was collected in plain test tubes to ensure sufficient serum volume after centrifugation. After blood collection, the sample was allowed to clot at room temperature for about 15–30 minutes. This helped separate the serum from cellular components. The blood samples were centrifuged at 3,000 rpm for 10 minutes at room temperature. After centrifugation, the serum was carefully separated to avoid hemolysis. Fresh samples of serum were used for determination of calcium, alkaline phosphatase and phosphorus. The remaining portion of serum samples were kept in a refrigerator for finding 25 (OH) D levels by ELISA at a later stage when 100 samples were collected and complete. Serum calcium, alkaline phosphatase and phosphorus were measured by using colorimetric method. All the analysis was done using Semi-Automatic Clinical Chemistry Analyzer Metrolab 1600.

Data analysis was conducted using SPSS (v. 26.0). Mean values were compared using t-tests, while logistic regression assessed the relationship between maternal vitamin D levels and infantile rickets.

Operational Definitions

Infantile Rickets: Defined as a condition characterized by softening and weakening of bones in infants due to vitamin D deficiency. Diagnosis was based on clinical &/or radiological signs and biochemical criteria, including elevated alkaline phosphatase levels (> 200 IU/L) and low serum calcium (< 8.5 mg/dL) or phosphate (< 3.5 mg/dL) levels (Wagner & Greer, 2019).

Healthy Infants: Defined as infants under one year of age who are clinically well, with no signs or symptoms of rickets, and with normal serum calcium, phosphate, and alkaline phosphatase levels.

Vitamin D Status (Maternal and Infant):
Deficient Vitamin D Level: Serum 25-hydroxyvitamin D (25[OH]D) concentration < 20 ng/mL for both mothers and infants, based on established thresholds indicating deficiency (Holick, 2017).
Sufficient Vitamin D Level: ≥ 20 ng/mL, indicating adequate vitamin D status.

Maternal Breastfeeding Status:
Defined as mothers exclusively breastfeeding their infants for at least six months or mixed feeding where breastfeeding remains the primary source of nutrition.

Biochemical Parameters:
Calcium (mg/dL): Serum calcium levels were measured for both mother-infant pairs. Hypocalcemia was defined as serum calcium levels below 8.5 mg/dL.
Phosphate (mg/dL): Serum phosphate levels were measured to assess phosphorus metabolism, with hypophosphatemia defined as levels below 3.5 mg/dL.

Alkaline Phosphatase (ALP) (IU/L): Levels were measured as an indicator of bone turnover and metabolism. Elevated ALP (>200 IU/L) in infants was suggestive of rickets.

Results

The average age of mothers in both groups was approximately 27.5 ± 3.8 years. Infants in both groups were similar in age, with an average of 8.3 ± 1.2 months. 40 mothers were vitamin D deficient; 32 (64%) were those of infants with rickets (Figure 1)

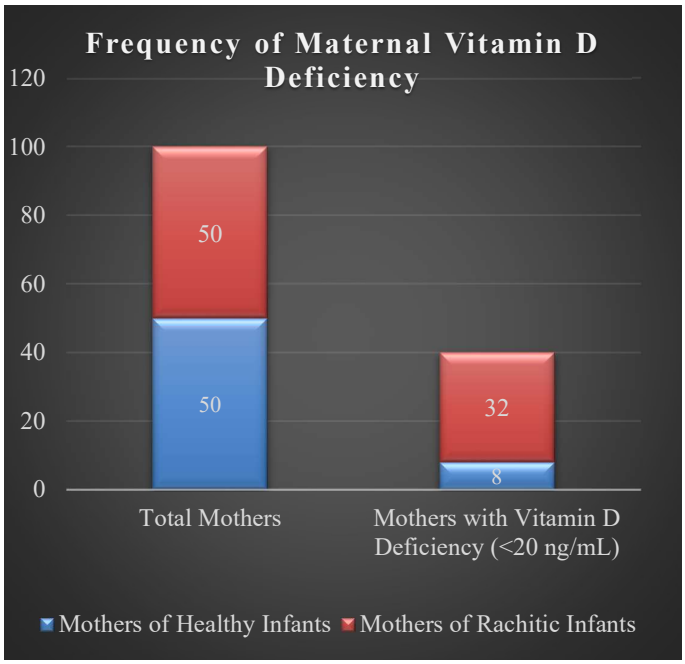

Table 1 presents the mean biochemical values for both groups, with t-tests conducted to assess significant differences:

Table 1: Comparison of Mean Biochemical Values Between Groups

Parameter	Healthy Infants Group (n=50)	Rachitic Infants Group (n=50)	Mean Difference	t-Value	p-Value
Maternal Vitamin D (ng/mL)	32.7 ± 5.5	18.5 ± 4.2	14.2	10.31	<0.001*
Infant Vitamin D (ng/mL)	26.3 ± 4.8	12.7 ± 3.5	13.6	11.29	<0.001*
Calcium (mg/dL)	9.8 ± 0.7	8.3 ± 0.9	1.5	9.42	<0.001*
Phosphate (mg/dL)	5.6 ± 0.8	4.2 ± 0.7	1.4	8.23	<0.001*
ALP (IU/L)	180 ± 22	290 ± 34	-110	-18.67	<0.001*

* Significant at $p < 0.05$

Table 2. Odds Ratios for Rickets Based on Maternal Vitamin D Deficiency

Maternal Vitamin D Status	Cases (Rachitic Infants)	Controls (Healthy Infants)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-Value
Deficient (<20 ng/mL)	32	8	12.00	4.96 - 29.06	<0.001*
Sufficient (>20 ng/mL)	18	42	1 (Reference)	-	-

* Statistically significant at $p < 0.05$

Mothers with vitamin D levels below 20 ng/mL were 12 times more likely to have infants diagnosed with rickets compared to mothers with sufficient vitamin D levels (OR = 12.00, 95% CI: 4.96 - 29.06, $p < 0.001$) as shown in Table 2. The reference category (sufficient maternal vitamin D) is used as the baseline comparison group, and by convention, it has an OR of 1. This strong association underscores the impact of maternal vitamin D deficiency as a significant risk factor for infantile rickets, suggesting the potential need for maternal supplementation during breastfeeding (Roth et al., 2020.

A multivariate logistic regression analysis was performed to evaluate maternal and infant biochemical factors associated with rickets risk, controlling for potential confounders (Table 3). Each 1 ng/mL increase in maternal vitamin D level was associated with an 8% decrease in the likelihood of infantile rickets (aOR = 0.92). Higher ALP levels in infants were significantly associated with rickets, indicating increased bone turnover in rachitic infants.

Table 3: Logistic Regression Analysis for Risk Factors of Infantile Rickets

Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-Value
Maternal Vitamin D (ng/mL)	0.92 per 1 ng/mL increase	0.88 - 0.96	<0.001*
Infant Vitamin D (ng/mL)	0.89 per 1 ng/mL increase	0.84 - 0.94	<0.001*
ALP (IU/L)	1.05 per 10 IU increase	1.02 - 1.08	<0.001*
Calcium (mg/dL)	0.74 per 1 mg/dL increase	0.65 - 0.82	<0.001*

* Significant at $p < 0.05$

A linear regression was conducted to examine the association between maternal vitamin D levels and key infant biochemical markers among the entire sample. Maternal vitamin D levels explained 68% of the variation in infant vitamin D levels ($R^2 = 0.68$), indicating a strong direct relationship. There was also a positive association with infant calcium and phosphate levels, though these associations were less pronounced.

Table 4. Linear Regression Analysis: Maternal Vitamin D and Infant Biochemical Markers

Dependent Variable	Beta Coefficient	95% Confidence Interval	R^2	p-Value
Infant Vitamin D (ng/mL)	0.78	0.67 - 0.89	0.68	<0.001*
Infant Calcium (mg/dL)	0.29	0.14 - 0.44	0.21	<0.001*
Infant Phosphate (mg/dL)	0.22	0.05 - 0.39	0.09	0.012

* Significant at $p < 0.05$

Discussion

The findings of this study align with existing literature. Our findings indicated that, most of the mothers of infants having rickets whose vitamin D levels were determined, were also vitamin D deficient. These mothers did not complain of any VDD symptoms at presentation. It can be presumed that these women would not otherwise have consulted to health care professionals. In our study, mothers with vitamin D levels below 20 ng/mL were 12 times more likely to have infants diagnosed with rickets compared to mothers with sufficient vitamin D levels (OR = 12.00, 95% CI: 4.96 - 29.06, $p < 0.001$). This finding aligns with previous studies[15-18] indicating that maternal vitamin D deficiency significantly increases the risk of rickets in exclusively breastfed infants due to insufficient vitamin D transfer through breast milk. Mothers at particular risk of VDD are those with reduced sun exposure for religious & cultural reasons (including *purdah*/veiling), dark pigmented skin, and inadequate intake of both vitamin D & calcium in their diet [5, 19].

Regarding infants, additional risk factors include maternal VDD and non-supplementation of vitamin D during breast feeding as shown in our study and those done by others [20].

In one of the studies [12], it has been shown that total metabolites of vitamin D in the plasma of mothers and that of fetus, are closely correlated which indicates that at the time of birth, stores of vitamin D in neonates depend upon those of mother. As a routine, since newborn infants are not generally exposed to sunlight directly and given that breast milk is lacking in & a poor source of vitamin D, even if normal at birth, vitamin D stores of the infant exclusively breastfed, may become depleted at the age of two months [21, 22].

Our study indicates a direct relationship between maternal VDD and the development of rickets in breastfed infants. Our study demonstrated that rachitic infants had mothers with significantly lower vitamin D levels compared to the healthy infant group, suggesting that insufficient maternal vitamin D during breastfeeding may be a major risk factor for infantile rickets.

Given the impact of maternal vitamin D levels on infant health, healthcare providers should consider maternal supplementation, particularly in populations at risk of deficiency. Routine screening for vitamin D deficiency in breastfeeding mothers could be instrumental in preventing rickets.

This study is limited by its sample size and reliance on a single hospital, which may affect generalizability. Additionally, dietary intake of calcium and exposure to sunlight were not controlled. Future research with larger sample sizes and controlled dietary variables is recommended. Longitudinal studies examining the effects of maternal vitamin D supplementation on infant health outcomes would further clarify this relationship.

Authors Contribution

Concept & Design of Study: **[1]Irfan Khan, [3]Shah Nawaz**

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Critical Review: [5]**Bushra Nabi,** [6]**Chaman Gul,** [7]**Zahid Irfan Marwat**
Final Approval of version: [1]**Irfan Khan,** [3]**Shah Nawaz**

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