Original Research Article

To evaluate the effect of Maternal Vitamin D Deficiency on Increased Risk for Hyperbilirubinemia in Term Newborns: an observational study

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Abstract

Aim: to study the effect of Maternal Vitamin D Deficiency on Increased Risk for Hyperbilirubinemia in Term Newborns. **Materials and Methods:** This prospective observational study was carried out in the Department of Pediatrics, Nalanda Medical College and Hospital at Patna, Bihar India from July 2019 to march 2020 .Serum 25-hydroxyvitamin D was measured from 200 included pregnant women during birth time. The level of bilirubin was measured in their newborns at 3rd to 5th days of life. **Results:** The level of 25-hydroxyvitamin D was low in 190 (95%) pregnant women. Hyperbilirubinemia was detected in 29 (14.5%) newborns at the 3rd to 5th days of life. Maternal vitamin D during pregnancy showed a significant correlation with the levels of bilirubin in newborns(r= -0.449, P<0.001). **Conclusion:** The presence of maternal vitamin D deficiency could effectively predict the increased risk for neonatal Hyperbilirubinemia.

Keywords: Hyperbilirubinemia, Jaundice, Mothers, Newborns, Vitamin D deficiency.

Introduction

Neonatal hyperbilirubinemia is one of the common entities that lead to frequent hospital admission of newborn. A peak serum bilirubin level of >12.9 occurs in 6.1% of healthy term newborn, and 3% develop a peak level of >15 mg/dl[1].Although the serum bilirubin level in most cases of neonatal hyperbilirubinemia is in the physiological range, which needs no treatment, some cases develop a peak serum bilirubin level, which, if not treated properly, may have devastating consequences on neonatal life. Kernicterus is one such complication in which a distinct yellowish pattern staining the brainstem, hippocampus, cerebellum, and certain brainstem nuclei (particularly the globus pallidus and subthalamic nucleus) is seen at autopsy in infants who die due to acute bilirubin toxicity. Most of sequelae of this disease arises from damage to these brain structures[2,3].

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Vitamin D is one of the fat-soluble vitamins technically considered a hormone. Many functions of vitamin D have been deciphered in medical research, where derangement can lead to cardiovascular, pulmonary, obesity, diabetes, and neoplastic dis- eases such as breast and colorectal carcinoma[4]. Increased inci- dence of many diseases including wheezing and asthma[5], acute disseminated encephalomyelitis (ADEM) and future multiple sclerosis[6], schizophrenia[7], irregular neurocognitive result[8], type 1 diabetes mellitus, and insulin resistance[9] has been correlated with decreased vitamin D concentration in pregnant women and their offspring. Advanced research has revealed the occurrence of 25-hydroxy vitamin D receptors on cells that have their actual origin from hepatic, neural, pancreatic, and genitourinary (pros- tate) systems. Immune system components such as lymphocytes and macrophages also contain vitamin D receptors[10].The major sources of vitamin D are through the skin and diet. Both these sources contain the inactive form of vitamin D. Its activation occurs in the liver and kidney by hydroxylation[11].Other cells that can synthesize vitamin D are monocytes and placenta during pregnancy[12]. A hypothetical relationship between vitamin D and bilirubin can be explained by the synthesis of both entities in the liver[13].Although the metabolism of both compounds occurs through different pathways in the liver, they can affect each other's metabolism, which remains to be proven[14].

Plenty of research is available on risk factors for neonatal hyperbilirubinemia, such as excessive hemolysis due to immune (ABO/Rh incompatibility) causes, nonimmune (hereditary spherocytosis, G6PD deficiency) causes, trauma (cephalohematoma), oxytocin, and diabetes in mothers. Limited number of studies is available on the relationship between hyperbilirubinemia and neonatal serum vitamin D[15]. Because of the fact that prevalence of maternal vitamin D deficiency is high in India and its probable effect on neonatal hyperbilirubinemia, the present study aimed to determine the effect of maternal vitamin D levels on increased risk of hyperbilirubinemia in their newborns.

Material and methods

This prospective observational study was carried out in the Department of Paediatrics in Nalanda Medical College and Hospital at Patna, Bihar India from july 2019 to March 2020, after taking the approval of the protocol review committee and institutional ethics committee. 200 pregnant women were included in this study.

Maternal information including age, gestational age, education, living area, hypothyroidism, and hypertension, type of delivery and history of vitamin D consumption during pregnancy was collected by interview and their medical files and also measured the mothers' heights and weights. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared of each mother on the day of interview. 5 mL of blood was obtained from each mother for measuring the level of calcium, phosphorus, alkaline phosphatase and 25- hydroxy vitamin D (25-OH vitamin D).

The newborns' weight, height and head circumference were measured by standard methods, and type of delivery; also, the method of feeding was recorded. The newborns were evaluated for hyperbilirubinemia at the 3rd to 5th days of life. Increase in the bilirubin level more than 12 mg/dl was considered as hyperbilirubinemia in the 3rd to 5th days of life.

Inclusion criteria

- Exclusive breast-fed babies
- In-born hospital-delivered babies
- Term healthy newborn babies > 37 weeks of gestation.

Exclusion criteria

- Newborn with major congenital abnormalities. Rh/ABO incompatibility
- Newborn with a history of perinatal asphyxia, meconium aspi- ration syndrome, pneumonia, sepsis, and conjugated hyperbilirubinemia.
- Pregnant women with a history of renal, hepatic, gestational diabetes, or hypertension and metabolic bone diseases

Methodology

The level of serum 25-OH vitamin D was measured using RIA (Radio-Immuno- Assay) method. For vitamin D, ranges <10 ng/mL were regarded as deficient, 10-30 ng/mL as insufficient, and >30 ng/mL as sufficient based on its brochures and those reported by Mayo Medical Laboratories [16]. The measurement of calcium, phosphorus and alkaline phosphatase was carried out using Pars Azmoon kits. Likewise, for calcium, the range of 8.5-10.5 mg/dL was regarded as normal and <8.5 mg/dL as deficient[17]. The determination of bilirubin was performed by photometric method, using 2, 4- dichloroaniline in the serum of venous blood samples at 3rd to 5th days of life.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and means. Statistical test applied for the analysis was student t-test.

Results

Table 1: Baseline characteristics of the 200 studied pregnant women

Parameter	Mean (Sd)
Weight (kg)	72.6 (11.4)
Height (cm)	160 (5.2)
Body mass index (kg/m^2)	31.0(4.2)
Gestational age (week)	38.7(0.9)
Area	
Urban area	163(81.5%)

Rural area	37 (18.5%)
Education	
12th standard	80 (40%)
graduate and post graduate	120 (60%)
Sufficient Serum Calcium	117 (58.5%)
Hypocalcaemia serum calcium below 8.5 mg/dL	83 (41.5%)
Serum phosphorus sufficient	172 (86%)
Alkaline phosphatase sufficient	171 (85.5%)
Vitamin D used by pregnant women	169 (84.5%)
Mode of delivery	
Vaginal delivery	125 (62.5)
Cesarean section	75 (37.5)

Table 2: Vitamin D deficiency with range in pregnant women

Vitamin D deficiency range	pregnant women
<10 ng/mL	33 (16.5%)
10-30 ng/mL insufficient level	157 (78.5%),
Sufficient level	10 (5%)

Table 3: Baseline characteristics of Term Newborns

Parameter	Mean (SD)	Minimum	Maximum
Birth weight (grams)	3088.6±348.5	2,970	4,600
Birth height (cm)	48.8± 2.18	41	58
Head circumference (cm)	33.89 ±1.07	31	37
level of bilirubin newborns at the 3rd to 5th days (Hyperbilirubinemia >12)	29 (14.5%)		

Discussion

The present study revealed that maternal vitamin D had a significant correlation with the levels of bilirubin of 3rd to 5th days of life in the newborns. Few case-controlled studies could show the association between maternal vitamin D deficiency and jaundice in newborns. In a study by Aletayeb et al., it was shown that there was an association between low serum vitamin D levels in mothers with jaundice in their newborns[18]. Multu et al., conducted a study on 51 newborns including 30 newborns with jaundice and 21 as the control; they found a strong relationship between neonatal vitamin D and jaundice (p=0.01)[19]. In contrast, Mehrpisheh et al. reported no significant relationship among 30 term-newborns with jaundice, in comparison with 30 control groups for neonatal vitamin D deficiency[20].

In present study, the association between maternal vitamin D deficiency and the increased risk for neonatal jaundice may be explained by focus on a common pathway in the liver for synthesis of vitamin D and for metabolism of bilirubin.

This study indicated the prevalence of hyperbilirubinemia was 14.5% in mature newborns at the 3rd to 5th days of life. The incidence of referral for neonatal jaundice was 10.5% of live term births in Turkey[21]. A multi-center study in six developing countries showed hyperbilirubinemia was a primary diagnosis for hospital admission in (78%) of the admissions in the first 6 days of life[22]. Worldwide, it is estimated that 10.5% of live birth newborns require phototherapy for jaundice[23]. Glucose-6- phosphate Dehydrogenase (G6PD) deficiency is a common cause of neonatal jaundice throughout the world; it is noteworthy that the higher rate of G6PD deficiency in this region is one of the reasons for the higher neonates' hyperbilirubinemia[24].The prevalence of vitamin D deficiency has been reported in pregnant women in different countries from 18% in UK to 84% in Netherlands, and the rate of 80% in Iran[25-27]. Considering the deficiency and insufficiency levels of vitamin D, we found that (16.5%) and (78.5%),of the mothers had low vitamin D in order.

It appears that sunny weather itself is not enough for protection against low vitamin D in pregnant mothers; outdoor activities, dressing habits, and dietary supplements have to be notified.

We found a relationship between the mother's education and the level of vitamin D similar to Scholl et al.'s study; it appears that educated mother's pay more attention to food fortification and use regular supplementation[28].It is important to remember that while sunscreen protects the individuals from sunlight, blocking these UV rays can predispose them, especially pregnant women, to vitamin D deficiency. As reported, vitamin D is negatively associated with a BMI of 85 kg/m^2 or higher[29].

The effect of vitamin D on BMI was not significant in our study. There was a correlation among the levels of maternal vitamin D with calcium, phosphorus and alkaline phosphatase. Vitamin D stimulates the transport of calcium and phosphorus into the extracellular fluid in the intestine, bone, and kidney; however, the production of the hormone is regulated directly or indirectly by plasma levels of calcium and phosphorus[30].

In contrast to our study, Shaheen et al. found vitamin D levels may not be correlated with the serum levels of alkaline phosphatise[31]. Vitamin D deficiency has been highlighted as a public health issue in recent years.

Approximately 85% of our mothers reported using vitamin D supplement; therefore, we suggest that new high strength vitamin D products should be prescribed for pregnant women in future. The strength of this study was large sample size compared to previous studies; it could help to better detect the statistical differences. Research that is more extensive is needed to generalize the result of this study.

Conclusion

The results of this study showed that the presence of maternal vitamin D deficiency could effectively predict the increased risk for neonatal jaundice. Vitamin D deficiency is common in pregnant women; researchers should be encouraged to study new high strength vitamin D supplements for preventing maternal hypovitaminosis D and following neonatal jaundice

References

1. Causes and outcome of young infant admissions to a Kenyan district hospital. Arch Dis Child 2003 May 1;88(5):438e43.
2. Hochberg Z. Rickets-past and present. In: Hochberg Z, editor. Vitamin D and rickets. Switzerland: Karger Publishers; 2003. p. 1e3.
3. Fanaroff AAM, Fanaroff RJAA, Martin RJ. Neonatal-perinatal medicine: diseases of the fetus and infant. Missouri: Mosby; 2002. p. 1123e34.
4. Özkan B, Döneray H. The non-skeletal effects of vitamin D. Çocuk Sagligi veHast Derg 2011;53:99e119.
5. Wong R, Desandre G, Sibley E, et al. Neonatal jaundice and liver disease. In: Martin R, Fanoroff A, Walsh M, editors. Fanaroff and Martin's neonatal- Peinatal medicine diseases of the fetus and infant. Philadelphia: Mosby Elsevier; 2006. p. 1419e65.
6. Aletayeb SM, Dehdashtiyan M, Aminzadeh M, Malekyan A, Jafrasteh S. Com- parison between maternal and neonatal serum vitamin D levels in term jaundiced and nonjaundiced cases. J Chin Med Assoc 2016 Nov 1;79(11): 614e7.
7. Coherity JP, Eichenwald EC, Hansen AR, Martin CR. Cloherty and Stark's manual of newborn care: neonatal hyperbilirubinemia. seventh ed. Philadel- phia: Wolter Kluwer; 2008. p. 336e7.
8. Shapiro SM. Chronic bilirubin encephalopathy: diagnosis and outcome. Semin Fetal Neonatal Med 2010; 15(3): 157e63.
9. Volpe JJ. Neurology of the newborn. fifth ed. Philadelphia: W B Saunders; 2008. p. 619e51.
10. Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, Zheng SG. Vitamin D and chronic diseases. Aging Dis 2017 May;8(3):346.
11. Morales E, Romieu I, Guerra S, Ballester F, Rebagliato M, Vioque J, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. Epidemiology 2012; Jan 1: 64e71.
12. Mirzaei F, Michels KB, Munger K, O'Reilly E, Chitnis T, Forman MR, et al. Gestational vitamin D and the risk of multiple sclerosis in offspring. Ann Neurol 2011; Jul;70(1):30e40.
13. McGrath JJ, Burne TH, Féron F, Mackay-Sim A, Eyles DW. Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. Schizophr Bull 2010; Sep 10;36(6):1073e8.
14. Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. Pediatrics 2012 Mar 1;129(3):485e93.
15. Sørensen IM, Joner G, Jenum PA, Eskild A, Torjesen PA, Stene LC. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the

offspring. Diabetes 2012 Jan 1;61(1) :175e8.
16. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc. 2010; 85(8):752–8.
17. Fong J, Khan A. Hypocalcemia: updates in diagnosis and management for primary care. Can Fam Physician. 2012;58(2):158–62.
18. Aletayeb SM, Dehdashtiyan M, Aminzadeh M, Malekyan A, Jafrasteh S. Comparison between maternal and neonatal serum vitamin D levels in term jaundiced and nonjaundiced cases. J Chin Med Assoc. 2016; 79(11):614-7.
19. Mutlu M, Çayir A, Çayir Y, €Ozkan B, Aslan Y. Vitamin D and hyperbilirubinaemia in neonates. HK J Paediatr 2013; 18:77-81.
20. Mehrpisheh S, Memarian A, Mahyar A, Valiahdi NS. Correlation between serum vitamin D level and neonatal indirect hyperbilirubinemia. BMC Pediatr. 2018; 26; 18(1):178.
21. Sarici SU, Serdar MA, Korkmaz A, Erdem G, Oran O, Tekinalp G, et al. Incidence, course, and predition of hyperbilirubinemia in near-term and term newborns. Pediatrics. 2004; 113(4):775-80.
22. Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet. 2008; 12; 371(9607):135–42
23. Bhutani VK. Editorial: building evidence to manage newborn jaundice worldwide. Indian J Pediatr. 2012;79(2):253-5.
24. Amoozegar V, Mirshakeri V, PaishvaN Prevalence of Glucose -6 - Phosphate Dehydrogenase Deficiency among Male Donors in Shiraz, Southern Iran. Iran J Med Sci. 2005; 30(2):94–6.
25. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Maternal vitamin D status during pregnancy and childhood bone mass at 9 years: a longitudinal study. Lancet. 2006; 7; 367(9504):36-43.
26. Van der Meer I, Karamali N, Boeke A. High prevalence of vitamin D deficiency in pregnant non-Western women in The Hague, Netherlands. Am J Clin Nutr 2006; 84(2):350- 3.
27. Bassir M, Laborie S, Lapillonne A, Claris O, Chappuis MC, Salle BL.Vitamin D deficiency in Iranian mothers and their neonates: a pilot study. Acta Paediatr. 2001; 90(5):577-9.
28. Scholl TO, Chen X. Vitamin D intake during pregnancy: association with maternal characteristics and infant birth weight. Early Hum Dev. 2009; 85(4):231-4.
29. Kumaratne M, Early G, Cisneros J. Vitamin D deficiency and association with body mass index and lipid levels in Hispanic American adolescents. Glob Pediatr Health. 2017;4: 2333794X17744141.
30. DeLuca HF. The control of calcium and phosphorus metabolism by the vitamin D endocrine system. Ann N Y Acad Sci. 1980; 355:1-17.
31. Shaheen S, Noor SS, Barakzai Q. Serum alkaline phosphatase screening for vitamin D deficiency states. J Coll Physicians Surg Pak. 2012; 22(7): 424-7.

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