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The effect of Maternal Vitamin D Deficiency on Increased Risk for Hyperbilirubinemia in Term Newborns

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Abstract

Background
Neonatal jaundice is prevalent, and the presence of hyperbilirubinemia frequently requires medical attention and hospital readmission. The aim of the present study was to determine the effect of maternal vitamin D deficiency on increased risk for hyperbilirubinemia in term newborns.

Materials and Methods
: This cross-sectional study was conducted on all pregnant women with gestational age of 38-42 weeks from southwestern Iran who referred to Hafez Hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran, from March 2018 to August 2018. Serum 25-hydroxyvitamin D was measured from 300 included pregnant women during birth time. The level of bilirubin was measured in their newborns at 3rd to 5th days of life. The obtained data were analyzed using SPSS software version 22.0.

Results
The level of 25-hydroxyvitamin D was low in 277 (92.3%) pregnant women. Hyperbilirubinemia was detected in 38 (12.6%) 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 ($r = -0.458$, $P<0.001$).
Conclusion

The results of this study showed that maternal vitamin D deficiency could be associated with the increased risk for neonatal hyperbilirubinemia.

Key Words: Hyperbilirubinemia, Jaundice, Mothers, Newborns, Vitamin D deficiency.

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1- INTRODUCTION

The production of bilirubin was started with catabolism of red blood cells via a series of enzymatic reactions in the reticuloendothelial cells (1). Significant elevation of bilirubin develops in approximately 60% of term infants and 80% of preterm ones during the first week of life (2, 3). Although bilirubin has a physiologic role as an antioxidant, high levels of unconjugated bilirubin is neurotoxic and can induce acute bilirubin encephalopathy or kernicterus in newborns. Some reasons for hyperbilirubinemia in newborns are hemolytic anemia, infection, hypoxia and prematurity. There are many risk factors for development of hyperbilirubinemia such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, blood group incompatibility, gestational age 35-36 weeks, and male gender (4-8).

Synthesis of vitamin D in nature depends on the effect of Ultraviolet (UV) radiation on the skin tissue and subsequent activation in the liver and in kidney (9). The potential sources of vitamin D in newborns are maternal vitamin D, which crosses the placenta, infant vitamin D supplements, milk formula, and breast milk. Various researches indicate that the prevalence of vitamin D deficiency in pregnant women ranged from 18% to 84% and in their newborn 36% to 70% depending on ethnicity, region, culture and customs in different countries (10). Low vitamin D levels in infants results in increased possibility of low birth weight, eczema, early-onset sepsis, and rickets (11-14). Observational studies have reported a higher rate of hyperbilirubinemia in newborns of mothers with vitamin D deficiency (15, 16). The prevalence of vitamin D deficiency in Iranian pregnant women is estimated 60% (10), and the rate of neonatal severe hyperbilirubinemia was 15% in this area (17). Because of the fact that prevalence of maternal vitamin D deficiency is high in Iran 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.

2- MATERIALS AND METHODS

2-1. Study design and population

All pregnant women with gestational age of 38-42 weeks who referred to Hafez Hospital affiliated to Shiraz University of Medical Sciences, Iran, from March 2018 to August 2018 were recruited in this cross-sectional study, using convenient sampling method. The sample size was determined to be 300 pregnant mothers with their newborns based on other studies in which the prevalence of hyperbilirubinemia (not severe) in Southern Iran was estimated to be about 73% in neonates (17). The sampling procedure continued until the required number of participants agreed to take part in the study.

2-2. Methods

Maternal information about baseline characteristics including age, gestational age, education, living area (urban or rural), hypothyroidism, and hypertension, type of delivery and history of vitamin D consumption during pregnancy was collected by interview and their medical files. An expert nurse 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. In the delivery room, 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 (18).

2-3. Laboratory measurements

The level of serum 25-OH vitamin D was measured using RIA (Radio-Immuno-Assay) method (Diasys GmbH, Germany). 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 (19). The measurement of calcium, phosphorus and alkaline phosphatase was carried out using Pars Azmoon kits (Pars Azmoon, Tehran, Iran). Likewise, for calcium, the range of 8.5-10.5 mg/dL was regarded as normal and <8.5 mg/dL as deficient (20). 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.

2-4. Ethical consideration

The Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1394.s332) approved this study. The design and objectives of the study were explained to the neonates' mothers, and written informed consent was obtained from those who were willing to participate in the study. However, they were assured that they could withdraw from the study whenever they intended, and it was explained to them that their data would be kept confidential and anonymous.

2-5. Exclusion criteria

Pregnant women with a history of renal, hepatic, gestational diabetes, or hypertension and metabolic bone diseases and those under treatment with oral corticosteroid and anticonvulsant drugs were excluded from the study. Newborns with pathological causes for their hyperbilirubinemia such as blood group mismatch, infection, polycythemia, and cephalic hematoma; a history of asphyxia; or apparent congenital anomalies were excluded. Additionally, neonates who had taken home phototherapy before referring to us were excluded from the study.

2-6. Data Analyses

The obtained data were analyzed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA) and statistical significance was set at $p<0.05$. Data are presented as mean $\pm$ standard deviation (SD) for quantitative variables and percentage for categorical variables. We used independent sample t-test for comparing the means and Pearson correlation coefficient was done for assessing the association of maternal vitamin D with neonatal bilirubin.

3- RESULTS

300 pregnant mothers in the age range of 17 to 41 years with the mean age of 29.05 ± 5.02 years were included in this study. **Table.1** presents the main demographic characteristics of the pregnant women. Vitamin D deficiency with range <10 ng/mL was detected in 44(14.6%), insufficient level of 10-30 ng/mL in 233(77.7%), and sufficient level in 23(7.7%) pregnant women. Serum calcium was sufficient in 169(56.4%); while 131(43.6%) of them had hypocalcaemia below 8.5 mg/dL. There was no significant relationship between maternal vitamin D and BMI (P=0.1). Based on the living area, 235(78.3%) mothers were living in the urban area. Among 300 pregnant women, 96(32%) had a degree under diploma, 145(48.3%) diploma, and only 59(19.6%) had a university degree. There was a correlation between maternal vitamin D and the level of their education (P< 0.001).

There was a correlation between the level of maternal vitamin D with calcium, phosphorus and alkaline phosphatase of mothers (P< 0.001 each). They reported the use of vitamin D during pregnancy in 259 (86.3%) mothers. Three hundred (150 girls and 150 boys) newborns who were delivered by the pregnant women were included in this study. The mean of birth weight in these newborns was 3097.6±352.5 grams, ranging from 2,980 to 4,500 grams; the mean of birth height was 49.2± 2.09 cm, ranging from 42 to 57 cm; and the mean of head circumference was 33.96 ±1.09 cm, ranging from 30 to 38 cm. Also, two-thirds (n=225) of the newborns had been born by vaginal delivery and one-third (n=75) by cesarean section. The number of breastfed newborns was 234 (87%) and the remaining 66 (22%) were formula fed. The level of bilirubin more than 12 was detected in 38(12.6%) newborns at the 3rd to 5th days of life as hyperbilirubinemia. Maternal vitamin D showed a significant correlation with the levels of bilirubin of the 3rd to 5th days of life in these newborns (r=- 0.458, P<0.001) (**Figure.1**); moreover, the level of maternal calcium, phosphorus and alkaline phosphatase was not associated with bilirubin of the 3rd-5th days of life (P= 0.1, P=0.1 and P=0.08, respectively).

Table-1: Baseline characteristics of the 300 studied pregnant women.

Parameter	Mean (SD)	Minimum	Maximum
Weight (kg)	72.6 (11.4)	52	116
Height (cm)	160 (5.2)	148	175
Body mass index (kg/m^2)	31.0(4.2)	21.1	45.5
Gestational age (week)	38.7(0.9)	36	41
Serum vitamin D (ng/mL)	18.4(9.5)	2.7	73.3
Serum calcium(mg/dL)	8.6(1.6)	3.1	35
Serum phosphorus (mg/dL)	3.7(0.6)	2	7.8
Alkaline phosphatase	337.4(115.1)	5.1	783

SD: Standard deviation.

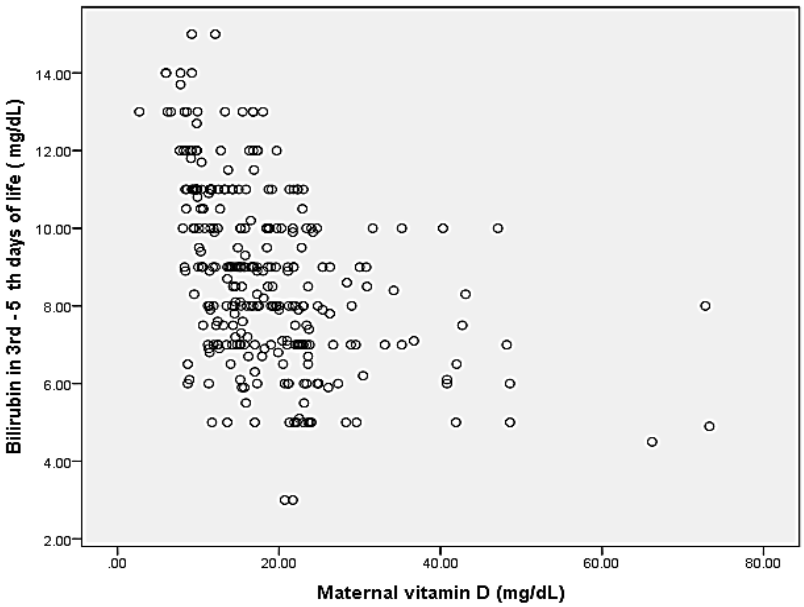

Fig.1: Correlation between the level of maternal vitamin D and neonatal bilirubin at the 3rd- 5th days of life.

4- 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 (15). 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) (16). 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 (21). 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 12.6% 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 (22). A multi-center study in six developing countries showed hyperbilirubinemia was a primary diagnosis for hospital admission in 12-78% of the admissions in the first 6 days of life (23). Worldwide, it is estimated that 10.5% of live birth newborns require phototherapy for jaundice (24). 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 (25). 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 (26-28). Considering the deficiency and insufficiency levels of vitamin D, we found that 14.6% and 77.7% 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 (29). 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 (30). 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 (31). In contrast to our study, Shaheen et al. found vitamin D levels may not be correlated with the serum levels of alkaline phosphatase (32). 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.

5- 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.

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7- CONFLICT OF INTEREST: None.

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