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The association between Vitamin D deficiency of the mother and the newborn with neonatal hyperbilirubinemia: A case-control study

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Abstract

Background: Very few studies have evaluated the possible relationship of Vitamin D / (25(OH)D) deficiency (VDD) of the mother and the newborn with neonatal jaundice. If VDD is determined as a predisposing risk factor (RF) for neonatal jaundice and affects the frequency of its occurrence, the detection of this deficiency may prove effective in predicting the onset of neonatal jaundice but also in significantly preventing it and therefore reducing morbidity and mortality from neonatal hyperbilirubinemia.

Materials and Methods: We conducted a study of 246 newborns and their Greek mothers, who were born in the obstetrics and gynecology clinic of Tzaneio Hospital of Piraeus, from September 2019 until January 2022. Results of total bilirubin (TBIL) and 25(OH)D vitamin levels are presented as means ± standard deviations (SD) or as frequencies and percentages. Chi-Square Test was used to find an association between maternal and neonatal 25(OH)D concentrations with TBIL. P value (P) <0.05 indicated a statistically significant association.

Results: The results of the study showed that, there does not seem to be a statistically significant correlation of VDD of both the maternal and the neonatal vitamin's D results with neonatal hyperbilirubinemia, as neither newborns with a low risk of hyperbilirubinemia, nor those with a moderate and high risk of hyperbilirubinemia had a higher risk of neonatal jaundice. Accordingly, maternal VDD before delivery was not shown to affect rates of neonatal jaundice.

Conclusions: In conclusion, it was observed that newborns who themselves or their mothers have VDD are not at greater risk of the adverse effects of neonatal jaundice.

Keywords: Pregnancy; Vitamin D; Bilirubin; Neonatal jaundice

1. Introduction

Vitamin D (25-hydroxyvitamin D/25(OH)D) is a fat-soluble vitamin with numerous actions that are not only related to bone health and calcium metabolism [1]. A few studies have also evaluated the possible association between VDD of the mother or the newborn with neonatal jaundice [2, 3, 4]. Huang et al [4] showed that vitamin D level of newborns with hyperbilirubinemia is 7.1 ng/ml lower than that of healthy newborns. A hypothetical relationship between vitamin D and bilirubin can be explained by the synthesis of both entities in the liver [2], 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 [2]. Aletayeb et al [3] studied bilirubin and additional factors that could potentially be related to vitamin D, such as calcium (Ca), phosphorus (P), alkaline phosphatic salts (Alkaline phosphatase/ALP's) and parathyroid hormone

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(PTH), but none seemed to be statistically significantly correlated with the mother's and her newborn vitamin D levels. Currently, as there are other studies that do not confirm this correlation [5], there is an ambiguity concerning a possible association between them, thus, this correlation remains to be elucidated. Very few studies have evaluated this relationship and further research is necessary.

Neonatal hyperbilirubinemia leads to jaundice of the newborn, defined as the supple complexion of the skin and its conjunctiva [6]. It is caused by an imbalance between the production and conjugation of bilirubin [7]. While approximately 60% of term and 80% of preterm newborns develop clinical jaundice in the first week [4, 8] after birth, in most cases, it is a mild, transient, and self-limiting condition and disappears without treatment referred to as physiological jaundice [8]. Moderately preterm infants, 30 to 35 weeks gestatonal age (GA) remain at increased risk for adverse outcomes, including acute bilirubin encephalopathy (ABE) relative to term infants [9]. Due to the possible toxicity of bilirubin, newborns should be monitored to avoid major neurological problems [10]. Knowing that a total serum bilirubin (TSB) or for others total plasma bilirubin (TBIL) level is not the most precise indicator of neurotoxicity, the role of expanded biomarkers or a "bilirubin panel" has yet to be validated in prospective studies [10]. Olusanya et al [11] found a wide variation in the number and type of risk factors (RFs) associated with severe neonatal hyperbilirubinemia. Boskabadi et al [12] considered in their study that the most common maternal RFs for neonatal jaundice were prematurity, blood type incompatibilities, preeclampsia, hypertension, diabetes mellitus, vaginal bleeding, delivery problems (type of delivery, labor injuries, delivery at home, skin ecchymosis and cephalohematoma), mothers and community cultural beliefs (use of traditional supplements), breast problems and decrease in breastfeeding [12]. Olusanya et al [11] determined perinatal and neonatal factors include gender, birth asphyxia, multiple gestation, GA <37 weeks, infection or elevated bilirubin levels in the first hours of life, severe anemia, acidosis, low birth weight, hypothermia, free bilirubin and serum aflatoxin [11]. In general, a number of other predisposing factors in the occurrence of jaundice are reported such as maternal diabetes, race, prematurity, height, male sex, drugs, trisomy 21, delayed meconium passage and family history of jaundice [11]. Type of delivery can be among the controversial factors [13]. The first step in prevention of all of these are the identification of predisposing factors.

This study was carried out in order to evaluate the relationship and investigate a possible association between maternal - neonatal 25(OH)D concentrations in serum, with neonatal hyperbilirubinemia, in newborns, of Greek mothers. If we identify with this study maternal or neonatal VDD as one more predisposing factor in predicting the occurrence and prevention of such risks in neonates, it would be important in reducing morbidity and mortality of hyperbilirubinemia. Diagnosis and timely treatment of neonatal jaundice for the prevention of dangerous side effects of pathological neonatal jaundice remain a serious debate.

2. Materials and methods

We conducted a study of 246 newborns and their Greek mothers, who were born in the obstetrics and gynecology clinic of Tzaneio Hospital of Piraeus, from September 2019 to January 2022. The criteria for participation in the present study were newborns born in the maternity clinic of the Tzaneio General Hospital of Piraeus, from Greek mothers, in any way of childbirth. The exclusion criteria were women who were taking medicine that could potentially affect vitamin D levels (corticosteroids, anticonvulsants, antituberculars, antifungals), or were being given higher doses of supplement 25(OH)D (>800 IU). Also excluded were pregnant women with a known history of rheumatoid arthritis, thyroid, parathyroid or adrenal disorders, liver or kidney failure, metabolic bone disease, DM type 1 and malabsorption syndromes (pancreatic insufficiency, fibrocystic disease and celiac disease). The decisions for any medical intervention (bilirubin measurement, frequency of measurements, initiation of neonatal phototherapy (NNPT), etc.) were made by the responsible neonatologists of the Clinic in accordance with the current protocols for the treatment of neonatal jaundice and were in no way influenced by the researchers or by the purposes of the study. Since the study was conducted with the aim of determining whether there is an association between VDD and TBIL in newborns with jaundice, who need NNPT, we had to rely on specific sources that mark the start of NNPT internationally [14, 15]. These sources define which bilirubin values signal the initiation of NNPT [14, 15] and what is defined as VDD. We evaluated the effect of both the mother's and the newborn's VDD on neonatal jaundice while any predisposing RFs of neonatal hyperbilirubinemia were taken into account. Neonatal hyperbilirubinemia was evaluated based on the values of TBIL on the third day of life of the newborns, based on the hyperbilirubimemia detection diagrams adopted by our country and applied to its population. Since, the measurement of TBIL was done percutaneously, it was based on the diagram of Varvarigou et al [14]. This diagram of boundaries for the onset of NNPT was used by the Hellenic Neonatal Society to establish general principles and guidelines, as a single national recommendation, for the prevention, detection and treatment of hyperbilirubinemia, in newborns with GA ≥35 weeks, in order to clarify the limits of the onset of NNPT.

Neonates that were evaluated for bilirubin, were divided into three groups who based on the curves of Varvarigou et al [14], had elevated bilirubin values (outside the normal range) and needed NNPT while at the same time taking into

account the existence or not of RFs. The first group concerns newborns with a low risk of developing a high bilirubin value, requiring NNPT (≥38 weeks, without RFs). The second group concerns newborns with a moderate risk of developing a high bilirubin value, who require NNPT (≥38 weeks, with RFs) or (35-37 weeks, without RFs). Finally, the third group concerns newborns, with a higher risk of developing a high bilirubin value, who require NNPT (35-37 weeks, with RFs). Since, the measurement of TBIL was done percutaneously, it was based on the diagram of Varvarigou et al [14]. If it needed to be measured, with blood sampling, we used the diagram of Bhutani et al [15]. The TSB of the newborn diagram of Bhutani et al [15], was also used to assess the risk of severe hyperbilirubinemia, with an assessment of the risk of severe jaundice. According to the diagram, at 72 hours of life of the newborn, if the capillary bilirubin is <11 mg/dL, it carries a 0% risk of jaundice and simple monitoring of the newborn is recommended. If the bilirubin capillary level is between 11 - 13.5 mg/dL, there is a 2% risk and a repeat measurement of TBIL at 48 hours or a review by a pediatrician is recommended. If the bilirubin capillary level is between 13.5 - 16 mg/dL, signalling a 13% risk and a repeat measurement of TBIL within 24 hours is required. If the capillary bilirubin level is >16 mg/dL, repeat TBIL within 12 hours extend stay in the maternity hospital. The evaluation of the bilirubin in newborns was done on their third day of life, percutaneously, as we said, using a transdermal bilirubinometer, by the midwives of the department. The use of transdermal TBIL levels measurement is a reliable and easy to use method and has significantly reduced the frequency of blood collection for its measurement [16]. The transcutaneous bilirubin (TCB) levels were performed with the portable transdermal bilirubinometer BiliCheck (Philips Respironics, Koninklijke, Philips Electronics N.V, Eindhoven, the Netherlands), in appropriate lighting conditions and in accordance with the measurement recommendations of this device. TCB levels were repeated by blood serum level measurements (spectrometric method) of TSB levels when the transdermal measurement was ≥15 mg/dL in newborns that were under NNPT or the TBIL was at the limits of initiation of NNPT or exchange blood transfusion (EBT) and finally, if the measurement of TBIL was done in newborns, with jaundice during the first 24 hours. Serum bilirubin measurements by taking blood, were performed in two capillaries, through skin puncture and the average of the two measurements was obtained. The blood samples of the mother-newborn couple, in order to estimate the 25(OH)D of the serum, were taken again by the midwives, for the mothers upon arrival at the maternity hospital, along with the rest of the preoperative examination, before childbirth, and for the newborns, at birth, from the umbilical cord. The processing of blood samples was made by the biochemical laboratory of Tzaneio General Hospital of Piraeus.

The evaluation of maternal/neonatal vitamin D concentrations was made according to the American Endocrine Society. The parturients were divided into those by: a) adequate levels of vitamin 25(OH)D (>30 ng/ml) [17] b) deficiency of vitamin 25(OH)D (21-29 ng/ml) [17], c) lack of vitamin 25(OH)D (<20 ng/ml) [17]. Here, perhaps there is an another category d) of severe vitamin deficiency 25(OH)D (<12 ng/ml) that could be added, given a review by Amrein et al [18], which informed about the current situation, worldwide, regarding 25(OH)D and the risks arising from its severe lack, with a dramatic increase in the risk of mortality, infections, but also many other diseases [18]. The newborns of the mothers of each category were also divided into newborns with: a) adequate levels of vitamin 25(OH)D (>30 ng/ml) [19], b) vitamin 25(OH)D deficiency (16-29 ng/ml), c) lack of vitamin 25(OH)D (<15 ng/ml) [19] again according to the adequacy criteria of the American pediatric endocrine society. As in adults, one more category could be added: d) severe vitamin deficiency 25(OH)D (≤12.5 ng/ml) [20] or 25(OH)D (<10 ng/ml) given the most recent review of Braegger et al [21]. A deficiency and severe deficiency of 25(OH)D was defined for clinical hypovitaminosis. Data were processed using IBM SPSS statistics 26 software. Results of serum bilirubin and 25(OH)D vitamin levels are presented as means ± standard deviations (SD) or as frequencies and percentages. Quantitative results of 25(OH)D vitamin levels in the mother-newborn pair were replaced to qualitative variables assessing adequacy, lack, deficiency and severe deficiency of maternal and neonatal concentrations and thus defined in that way. In the same way, the quantitative results of bilirubin levels, in the mother-newborn pair, were reduced to qualitative variables and evaluated as jaundice, non-jaundice. Chi-Square Test was used to find an association between maternal and neonatal 25(OH)D concentrations. P <0.05 indicated a statistically significant association.

3. Results

In the first group of newborns, with a low risk of hyperbilirubinemia (≥38 weeks, without RFs) to initiate NNPT, there were 121 of the 246 newborns, 49% of the newborns of the study (Table 1). From these newborns, 47% (57/121) of them had a severe VDD, 14% (18/121) had a lack of 25(OH)D, 31% (38/121) had deficiency of 25(OH)D and 6% (8/121) had adequacy of 25(OH)D. From 61% of newborns with clinical hypovitaminosis 25(OH)D (severe deficiency, lack), only 1% (1/75) had high bilirubin values, which based on the curve of Varvarigou et al [14], needed NNPT, so the clinical hypovitaminosis 25(OH)D of newborns does not seem to be associated with high bilirubin values requiring NNPT, (P-value (P) =0.769). But also the VDD of the mother (Table 2), do not seem to be associated with high bilirubin values of the newborn (P =0.423), as from the 52% (64/121) of the mothers who had clinical hypovitaminosis 25(OH)D, only 1 of their respective 64 newborns, had an increased bilirubin value with the need to start NNPT.

In the second group of newborns, with a moderate risk of hyperbilirubinemia (≥38 weeks, with RFs) or (35-37 weeks without RFs) to initiate NNPT (Table 3), there were 80 of the 246 newborns (≥38 weeks, with RFs), 32% of the newborns of the study (Table 3.1). From these newborns, 50% (40/80) of them had a severe VDD, 20% (16/80) had a lack of 25(OH)D, 27% (22/80) had deficiency of 25(OH)D and 2,5% (2/80) had adequacy of 25(OH)D. From 70% (56/80) of newborns with clinical hypovitaminosis 25(OH)D only 12% (7/56) had high bilirubin values, which based on the curve of Varvarigou et al [14], needed NNPT. Therefore, the clinical hypovitaminosis 25(OH)D on the newborn's third day of life, does not seem to be associated with high bilirubin values requiring NNPT (P =0.720) (Table 3.1). 18 of the 246 newborns with a moderate risk of hyperbilirubinemia (35-37 weeks, without RFs) to initiate NNPT comprised 7% of the newborns of the study (Table 3.2). From these newborns, 61% (11/18) of them had a severe VDD, 11% (2/18) had a lack of 25(OH)D, 16% (3/18) had deficiency of 25(OH)D and 11% (2/18) had adequacy of 25(OH)D. From 72% (13/18) of newborns with clinical hypovitaminosis 25(OH)D, 0% (0/13) had high bilirubin values, which based on the curve of Varvarigou et al [14], needed NNPT (Table 3). Not here either, the clinical hypovitaminosis 25(OH)D of newborns does not seem to be associated with high bilirubin values requiring NNPT (P =0.151) (Table 3.2). Equally, there wasn' t correlation between the mother's vitamin D levels and neonatal hyperbilirubinemia in this group, neither for neonates ≥38 weeks with RFs, (P =0.263) (Table 4.1) nor for neonates 35-37 weeks, without RFs, (P =0.295) (Table 4.2).

Finally, in the third group of newborns, with a higher risk of hyperbilirubinemia (35-37 weeks with RFs) for starting NNPT, there were 27 of the 246 newborns, 10% of the newborns of the study (Table 5). 62% (17/27) of these newborns had clinical hypovitaminosis 25(OH)D, but only 17% (3/17) of them had an increased bilirubin value, with the need to start NNPT. No correlation between the mother's vitamin D levels and neonatal hyperbilirubinemia was also shown in, with 59% (16/27) of mothers who had clinical hypovitaminosis 25(OH)D, having newborns who by 11% (2/17) only, have increased bilirubin values with the need to start NNPT (Table 6). Therefore, the clinical hypovitaminosis 25(OH)D, both of the mothers (P =0.252) (Table 6) and the newborns (P =0.463) (Table 5), do not seem to be associated with high bilirubin values requiring NNPT.

Table 1 represents First group. Newborns with low risk for hyperbilirubinemia (≥38 weeks, without RFs) [14]. Association of clinical hypovitaminosis 25(OH)D of newborns above with their bilirubin values, for the start of NNPT, in the third 24 hours of life.

Table 1 Newborns with a low risk of hyperbilirubinemia (≥38 Weeks), without RFs

Neonate's vitamin D Bilirubin Crosstabulation				
Count				
		BILIRUBIN		Total
		Not jaundice	Jaundice*	
Neonate's Vitamin D	Severe deficiency	56	1	57
	Lack	18	0	18
	Deficiency	38	0	38
	Adequacy	8	0	8
Total		120	1	121

*In Table 1. For the sake of brevity, jaundice is defined as the point when the TBIL of newborns with a low risk, ≥38 Weeks, without RFs, is above the curve of the diagram (≥18 mg/dL), at 72 hours of life, indicating which babies need NNPT, while not jaundice is when the TBIL ≤18 mg/dL is below the diagram [14], at 72 hours of life, so they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.132	3	0.769
Likelihood Ratio	1.515	3	0.679
Linear-by-Linear Association	.907	1	0.341
N of Valid Cases	121		
The statistical significance is indicated in the table as positive when the P value ≤0.05			

Table 2 represents First group. Mother's of newborns with low risk for hyperbilirubinemia (≥38 weeks, without RFs) [14]. Association of clinical hypovitaminosis 25(OH)D of mothers above, with the bilirubin values of newborns for the start of NNPT, in the third 24 hours of life.

Table 2 Mother's of newborns with a low risk of hyperbilirubinemia (≥38 Weeks), without RFs

Mother's vitamin D Bilirubin Crosstabulation				
Count				
		Bilirubin		Total
		Non jaundice	Jaundice*	
Mother's vitamin D	Severe Deficiency	31	1	32
	Lack	32	0	32
	Deficiency	28	0	28
	Adequacy	29	0	29
Total		120	1	121

*In Table 2. For the sake of brevity, jaundice is defined as the point when the TBIL of newborns with little risk without RFs, is above the curve of the diagram (≥18 mg/dL), at 72 hours of life, indicating which babies need NNPT while not jaundice is when TBIL ≤18 mg/dL is below the diagram [14], at 72 hours of life, so they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	2.804	3	0.423
Likelihood Ratio	2.683	3	0.443
Linear-by-Linear Association	1.666	1	0.197
N of Valid Cases	121		
The statistical significance is indicated in the table as positive when the P value ≤0.05			

Table 3 represents Second group. Newborns with moderate risk for hyperbilirubinemia (≥38 weeks, with RFs) or (35-37 weeks, without RFs) [14]. Association of clinical hypovitaminosis 25(OH)D of newborns above with their bilirubin values, for the start of NNPT, in the third 24 hours of life.

Table 3 Newborns with a moderate risk of hyperbilirubinemia (≥38 weeks), with RFs

Neonate's vitamin D Bilirubin Crosstabulation				
Count				
		BILIRUBIN		Total
		Not jaundice	Jaundice*	
Neonate's Vitamin D	Severe deficiency	35	5	40
	Lack	14	2	16
	Deficiency	21	1	22
	Adequacy	2	0	2
Total		72	8	80

*In Table 3 For the sake of brevity, jaundice is defined as the point when the TBIL of newborns at moderate risk, ≥38 weeks, with RFs is above the curve of the diagram (≥15.5 mg/dL), at 72 hours of life, indicating which babies need NNPT while not jaundice is when TBIL ≤15.5 mg/dL is below the diagram [14], at 72 hours of life, when they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	1.338	3	0.720
Likelihood Ratio	1.679	3	0.642
Linear-by-Linear Association	1.098	1	0.295
N of Valid Cases	80		
The statistical significance is indicated in the table as positive when the P value ≤0.05			

Table 4 Newborns with a moderate risk of hyperbilirubinemia (35-37 Weeks), without RFs

Neonate's vitamin D Bilirubin Crosstabulation				
Count				
		BILIRUBIN		**Total**
		Not jaundice	Jaundice*	
Neonate's Vitamin D	Severe deficiency	11	0	11
	Lack	2	0	2
	Deficiency	2	1	3
	Adequacy	2	0	2
Total		17	1	18

*In Table 4 For the sake of brevity, jaundice is defined as the point when the TBIL of newborns with a moderate risk without RFs, is above the curve of the diagram (≥15.5 mg/dL), at 72 hours of life, indicating which babies need NNPT while not jaundice is when the TBIL ≤15.5 mg/dL is below the diagram [14], at 72 hours of life, so they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	5.294	3	0.151
Likelihood Ratio	3.905	3	0.272
Linear-by-Linear Association	1.274	1	0.259
N of Valid Cases	18		
The statistical significance is indicated in the table as positive when the P value ≤0.05			

Table 5 represents Second group. Mother's of newborns with moderate risk for hyperbilirubinemia (≥38 weeks, with RFs) or (35-37 weeks, without RFs) [14]. Association of clinical hypovitaminosis 25(OH)D of mothers above with their bilirubin values, for the start of NNPT, in the third 24 hours of life.

Table 5 Mother's of newborns with a moderate risk of hyperbilirubinemia (≥38 Weeks), with RFs

Mother's vitamin D Bilirubin Crosstabulation				
Count				
		Bilirubin		**Total**
		Non jaundice	Jaundice*	
Mother's Vitamin D	Severe Deficiency	20	1	21
	Lack	24	6	30
	Deficiency	19	1	20
	Adequacy	9	0	9
Total		72	8	80

*In Table 5. For the sake of brevity, jaundice is defined as the point when the TBIL of newborns at moderate risk with RFs is above the curve of the diagram (≥15.5 mg/dL), at 72 hours of life, indicating which babies need NNPT while not jaundice is when TBIL ≤15.5 mg/dL is below the diagram [14], at 72 hours of life, when they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	3.982	3	0.263
Likelihood Ratio	6.226	3	0.101
Linear-by-Linear Association	2.903	1	0.088
N of Valid Cases	80		
The statistical significance is indicated in the table as positive when the p value ≤0.05			

Table 6 Mother's of newborns with a moderate risk of hyperbilirubinemia (35-37 Weeks), without RFs

Mother's vitamin D Bilirubin Crosstabulation				
Count				
		Bilirubin		**Total**
		Non jaundice	**Jaundice***	
Mother's Vitamin D	Severe Deficiency	6	0	6
	Lack	3	1	4
	Deficiency	6	0	6
	Adequacy	2	0	2
Total		17	1	18

*In Table 6. For the sake of brevity, jaundice is defined as the point when the TBIL of newborns at moderate risk with RFs is above the curve of the diagram (≥15.5 mg/dL), at 72 hours of life, indicating which babies need NNPT while not jaundice is when TBIL ≤15.5 mg/dL is below the diagram [14], at 72 hours of life, when they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	3.706	3	0.295
Likelihood Ratio	3.225	3	0.358
Linear-by-Linear Association	.047	1	0.829
N of Valid Cases	18		
The statistical significance is indicated in the table as positive when the p value ≤0.05			

Table 7 represents Third group. Newborns with high risk for hyperbilirubinemia (35-37 weeks with RFs) [14]. Association of clinical hypovitaminosis 25(OH)D of newborns with their bilirubin values. Analysis in newborns above, for initiation of NNPT, in the third 24 hours of life.

Table 7 Newborns with a high risk of hyperbilirubinemia (35-37 weeks), with RFs

Neonate's vitamin D Bilirubin Crosstabulation				
Count				
		Bilirubin		**Total**
		Non jaundice	Jaundice*	
Neonate's Vitamin D	Severe Deficiency	9	2	11
	Lack	5	1	6
	Deficiency	5	4	9
	Adequacy	1	0	1
Total		20	7	27

*In Table 7. For the sake of brevity, jaundice is defined as the point when the TBIL of newborns at moderate risk with RFs is above the curve of the diagram (≥13.5 mg/dL), at 72 hours of life, indicating which babies need NNPT while not jaundice is when TBIL ≤13.5 mg/dL is below the diagram [14], at 72 hours of life, when they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	2.569	3	0.463
Likelihood Ratio	2.700	3	0.440
Linear-by-Linear Association	.836	1	0.361
N of Valid Cases	27		
The statistical significance is indicated in the table as positive when the p value ≤0.05			

Table 8 represents Third group. Mother's of newborns with high risk for hyperbilirubinemia (35-37 weeks, with RFs) [14]. Association of clinical hypovitaminosis 25(OH)D of mothers with the bilirubin values of their newborns. Analysis in newborns with a higher risk of hyperbilirubinemia (35-37 weeks, with RFs), for initiation of NNPT, in the third 24 hours of life.

Table 8 Mother's of newborns with a high risk of hyperbilirubinemia (35-37 Weeks), with RFs

Mother's vitamin D Bilirubin Crosstabulation				
Count				
		Bilirubin		Total
		Non jaundice	Jaundice*	
Mother's Vitamin D	Severe Deficiency	9	1	10
	Lack	5	1	6
	Deficiency	4	4	8
	Adequacy	2	1	3
Total		20	7	27

*In Table 8. For the sake of brevity, jaundice refers to when the TBIL of newborns at moderate risk with RFs is above the curve of the chart (≥13.5 mg/dL), at 72 hours of life, indicating which babies need NNPT and not jaundice when TBIL ≤13.5 mg/dL is below the diagram [14], at 72 hours of life, when they do not need NNPT.

Statistical significance was checked with Chi square test.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	4.089	3	0.252
Likelihood Ratio	4.085	3	0.252
Linear-by-Linear Association	2.678	1	0.102
N of Valid Cases	27		
The statistical significance is indicated in the table as positive when the p value ≤0.05			

4. Discussion

Some of the main advantages of this study were its prospective design, its satisfactory sample size and the fact that it involved a single population, the Greek. These allowed us the qualitative and quantitative analysis of the possible association of VDD, of the mother-newborn pair, with neonatal hyperbilirubinemia. Over time, most corresponding studies looked for mean values ± SD of maternal-neonatal 25(OH)D levels and corresponding values of neonatal bilirubin. However, these studies did not classify, like ours, vitamin D levels (adequacy, lack, deficiency, severe deficiency), but also they did not take into account, like we did, internationally recognized curves, to assess and evaluate the newborn hyperbilirubinemia, but they simply set specific values above which the neonate suffered from hyperbilirubinemia or subjectively assessed yellowish staining of the sclera and skin when the bilirubin exceeds the normal range, especially when the TBIL rised above 5 mg/dl [4]. Even worse, many of them excluded from their study neonates who had RFs for neonatal hyperbilirubinemia and did not take into account, like we did, the participation of RFs in the mechanism of development of neonatal hyperbilirubinemia. Only one study by Huang et al [4], evaluating the relationship between vitamin D levels and neonatal hyperbilirubinemia with a meta-analysis, included high-quality case-control studies that reduced bias and improved the reliability of the results, but the number of included articles were small, study population was newborns within one month of birth (compared to ours that studied on the third day) and they included diverse populations, thus impacting the quality of the research results. Four of the six included studies involved Asian populations. Different populations may have different results and are more likely to produce contradictory results. This is probably how we explain the opposite results of our study and theirs.

There did not appear to be an association between either maternal VDD and neonatal hyperbilirubinemia or between neonatal VDD with abnormal bilirubin levels. Therefore, VDD does not appear to be a RF for neonatal hyperbilirubinemia. Currently, assessment of the relationship between VDD and neonatal hyperbilirubinemia is unclear and controversial. Therefore, it is not possible to evaluate and design a preventive action plan for health professionals, with the aim of timely and effective taking of vitamin D supplements by pregnant women and newborns, which hypothetically could reduce the risk of neonatal hyperbilirubinemia. If it is finally proven, that VDD can affect the levels of neonatal bilirubin, important steps may be taken in the prevention, diagnosis and management of neonatal jaundice, as well as in avoiding its unwanted complications. If the aforementioned relationship holds true, perhaps it would be extremely helpful for health professionals to have a maternal screening test at the end of labor that could immediately diagnose newborns at risk of developing hyperbilirubinemia, as early treatment of neonatal jaundice for preventing the dangerous side effects of pathological neonatal jaundice would be extremely effective. There are few studies evaluating the mechanism of the relationship between VDD and neonatal hyperbilirubinemia. Probably, studying this correlation in different populations may produce different results, due to the specificity of vitamin D intake, according to region and ethnicity. In Greece, further studies are recommended, including follow-up studies after 15 days of age, where jaundice has usually gone away, and certainly, our findings should be investigated before vitamin D supplementation is started. So, in the future, further studies are deemed necessary that are more reliable and deal with a large multinational sample size.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest

Statement of ethical approval

The scientific council of Tzaneio Hospital, Piraeus resulted from elections concluded on 3/28/2018 and was constituded in a body with Act Number 5844 of 29-3-2018 of the Director of the hospital. The scientific council, in accordance with strictly observing conditions of anonymity and the provisions of the General Data Protection Regulation, granted approval to carry out a sample check on pregnant women, on the status of vitamin D.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study

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Author Contributions

AK conceived the topic; AK, MD, AL and GI retrieved the literature; AK wrote the paper; KB collected the results of the values of 25(OH)D; MD, AL, EA and GI provided relevant methodological support and supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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