Unveiling the Novel Impact of Vitamin D Injections at Birth on the Prognosis of Newborns: A Double-Blind Study

Hassan Boskabadi[1], Tahereh Sadeghi[2] and Mina Mostafavi[3]*

[1]Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Assistant Professor of Nursing, Department of Pediatrics, School of Nursing and Midwifery, Nursing and Midwifery Care Research Center, Akbar Hospital, Mashhad University of Medical Sciences, Mashhad Iran

[3]Resident of Pediatric, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad Iran

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*Corresponding author: Mina.mostafavi70@yahoo.com

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Abstract

Objectives: Vitamin D deficiency can harm both the infant and the mother, potentially altering the trajectory of the child's life. This study, therefore, aimed to delve into the potentially life-changing impact of Vitamin D intake at birth on the prognosis of newborns.

Methods: The present double-blind, randomized clinical trial study, conducted between 2021-2022, encompassed 100 infants who were admitted to the Neonatal Intensive Care Unit (NICU) of QAEM Hospital in Mashhad, Iran. Premature infants with a gestational age of less than 34 weeks and requiring hospitalization in the NICU were randomly allocated into two groups. The intervention group consisted of infants who received 10,000 units of Vitamin D, while the control group comprised infants who did not receive any Vitamin D at birth. The infants were evaluated based on clinical symptoms, the requirement and duration of oxygen therapy, the necessity and length of mechanical ventilation, the method of oxygen therapy administered, and the length of their hospital stay.

Results: This study included 100 infants, comprising 56 boys (56%) and 44 girls (44%). A significant difference was observed between the intervention and control groups regarding maternal age frequency (P=0.013). Additionally, the frequency of mechanical ventilation (P=0.03), surfactant administration (P=0.009), and the number of times surfactant was administered (P=0.02) also showed significant differences between both the intervention and control groups.

Conclusion: The current study's findings suggest that vitamin D intake at birth could potentially revolutionize the management of respiratory complications in premature infants, a crucial discovery for healthcare practitioners and researchers.

Keywords: Infant; Prematurity; Vitamin D, Respiratory distress, ventilation, surfactant

Introduction

Vitamin D plays a crucial role in various physiological processes, including bone health, immune function, and modulation of inflammatory responses.[1,2] Neonatal prognosis pertains to the likelihood of a newborn surviving and maintaining good health during the initial 28 days of life. In 2020, the decrease in global mortality rates for children under five years old was more significant than the decline in neonatal mortality rates. Almost half (47%) of all deaths among children under 5 occurred during the newborn period, which is defined as the first 28 days of life.[3]

The majority of neonatal deaths can be attributed to factors such as preterm birth, complications during delivery (like birth asphyxia), infections, or congenital defects. Most infants who die within the first 28 days of life succumb to conditions and diseases that result from insufficient quality care at birth and during the early days of life.[4] Ensuring high-quality antenatal care, skilled care during childbirth, postnatal care for mothers and infants, and specialized care for small and sick newborns can significantly enhance the survival and health of newborns. This approach can also help prevent avoidable stillbirths. Women who receive midwife-led continuity of care have a 16% lower risk of losing a baby and a 24% lower risk of experiencing preterm birth.[5]

Vitamin D is crucial in maintaining healthy bones and teeth, and its importance is heightened during pregnancy. Vitamin D deficiency is common during pregnancy and can result in abnormal bone growth, fractures, or even newborn rickets. Several studies have associated vitamin D deficiency with an increased risk of complications during pregnancy, such as gestational diabetes, preeclampsia, preterm birth, and low birth weight.[6] Low levels of vitamin D during pregnancy are linked to a range of health issues and various consequences, from the pre-implantation stage of the fetus to diseases in adulthood. It is currently recognized that a vitamin D deficiency in the mother can impact maternal and fetal calcium homeostasis. This deficiency also impacts the development of the fetus's bones.[7] Due to the rapid growth and development of the fetus, particularly the calcification of bones towards the end of pregnancy, pregnant mothers may be at risk of vitamin D deficiency. As the fetus and infant rely on the vitamin D levels in the mother's blood and breast milk, it is crucial to maintain sufficient reserves of vitamin D.[8]

The majority of premature infants suffer from vitamin D deficiency. This deficiency is found to be more pronounced in stillborn infants compared to those who survive. Hence, assessing the level of vitamin D in the umbilical cord could potentially aid in predicting the prognosis of premature infants. Furthermore, to enhance the health outcomes of both mothers and newborns, it is recommended that vitamin D supplementation be included as a standard part of prenatal care for all expectant mothers.[9]

Hence, a Vitamin D deficiency in expectant mothers can reduce this vital nutrient transfer to the fetus via the placenta. This deficiency can harm both the baby and the mother, potentially influencing the baby's health.[10] Recent research indicates that vitamin D deficiency in premature infants is linked to a host of complications, including infection, cerebral hemorrhage, retinopathy of prematurity, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and even mortality. Correcting the vitamin D levels in newborns could potentially reduce the incidence of some of these significant complications.[11-13] Hence, this study aimed to examine the impact of vitamin D intake at birth on neonatal outcomes.

Methods

The current double-blind clinical trial involved 100 infants admitted to the NICU of Ghaem Hospital in Mashhad, Iran, from 2021 to 2022. The inclusion criterion for this study was premature infants under 34 weeks old. On the other hand, the study excluded infants with noticeable congenital anomalies, congenital infections, those who died in the delivery room, as well as infants born to mothers with a history of drug abuse or asthma (Figure 1).

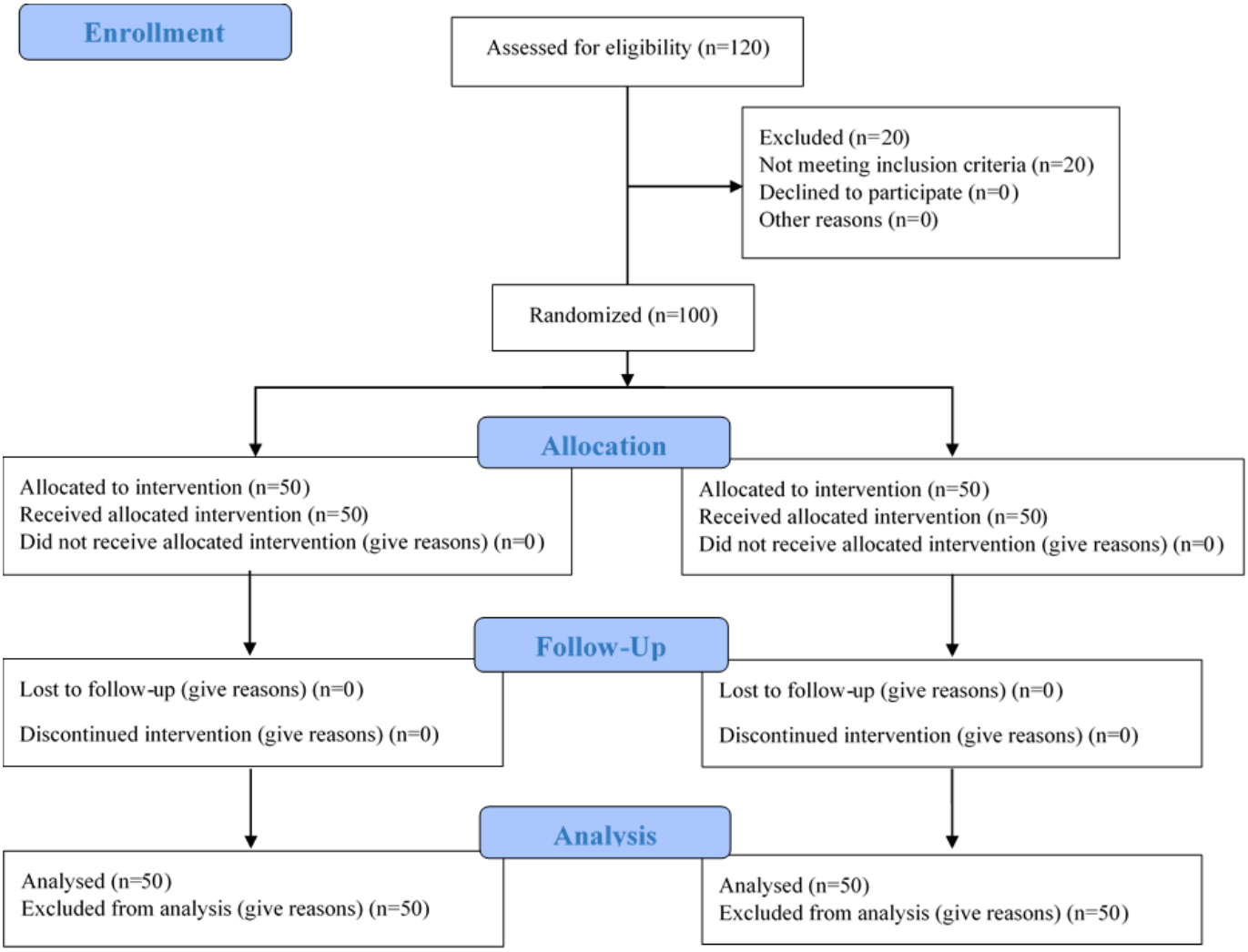

Figure 1: CONSORT Flow chart.

Based on the study by Holick et al.,[14] considering the 82% chance of premature infants experiencing respiratory distress that requires oxygen and assuming a 42% difference between the intervention and control groups, a sample size of 44 cases was estimated for each group. This estimation considered an alpha of 0.01 and a beta of 0.1. Ultimately, each group comprised 50 cases, considering a potential attrition rate of 10%.

The study included all premature infants who were less than 34 weeks of gestation and required hospitalization in the neonatal unit. Using a method of concealment, the participants were randomly divided into the intervention (n=50) and control (n=50) groups. This division was achieved through sealed envelopes and a random number table.

On the first day after birth, the intervention group was administered 10,000 units of vitamin D. In contrast, the control group did not receive any vitamin D supplementation at birth. Before the intervention, the newborns' blood samples were collected for routine tests, and their serum vitamin D levels were measured. The samples were prepared and centrifuged, after which the serum was stored at -20° before being sent for laboratory analysis. The vitamin D levels were assessed using an Elisa Reader (RT2100c, Germany) and an Elisa Washing machine, employing the ELISA method. Vitamin D deficiency was defined as values less than 30 nmol/l, while values greater than 30 nmol/l were deemed sufficient. Vitamin D deficiency was categorized into three groups: severe deficiency (levels below 10 ng/ml), moderate deficiency (levels between 10-20 ng/ml), and mild deficiency (levels ranging from 20-30 ng/ml).

As prescribed by the attending physician, the standard procedures were followed by routine practices for both groups. Infants were evaluated and compared between the two groups during hospitalization based on various parameters. These included clinical symptoms, oxygen requirements, duration of oxygen therapy, necessity and duration of mechanical ventilation, method of oxygen therapy, and occurrence of infection.

All analyses were conducted using SPSS software (version 22, Chicago, IL, USA). The descriptive data were presented as the Mean±SD and as a percentage. Before the analysis, the normality of the data was verified using the one-sample Kolmogorov-Smirnov Test. The data were analyzed using Student's t-test, Mann-Whitney U, and chi-square tests. A P-value of less than 0.05 determined statistical significance.

The study protocol received approval from the Ethics Committees of Mashhad University of Medical Sciences (Approval Number: IR.MUMS.MEDICAL.REC.1399.572). Additionally, the study was registered with the Iranian Registry for Clinical Trials (Registration Code: IRCT20110807007244N6).

Results

Twenty infants were excluded from the present study due to not meeting the inclusion criteria. The study included 100 infants, comprising 56 boys (56%) and 44 girls (44%). The intervention and control groups were homogeneous in terms of parity (P=0.44), gestational age (P=0.257), betamethasone administration (P=0.74), and Pregnancy complications (P>0.1) (Table 1). In both groups, the highest frequency corresponded to one pregnancy (P=0.44), one delivery (P=0.47), and the absence of pregnancy complications (P=0.200). Regarding the type of delivery, the rate of cesarean section in the control group was significantly higher than in the intervention group (P=0.02).

Table 1: Maternal Characteristics in the Intervention and Control Groups.

Variable		Intervention group (n=50)	Control group (n=50)	P-value
Gestational age (number) (%)	25-28 weeks	6 (12)	7 (14)	0.257*
	28-32 weeks	24 (48)	16 (32)	
	32-34 weeks	20 (40)	27 (54)	
Number of deliveries (number)(%)	One	20 (40)	21 (42)	0.44*
	Two	13 (26)	8 (16)	
	Three and more	17 (34)	21 (42)	
Prenatal care (number) (%)	Zero	24 (48)	26 (52)	0.47*
	One	14 (28)	9 (18)	
	Two and more	15 (30)	12 (24)	
	Yes	49 (98)	49 (98)	0.99*
	No	1 (2)	1 (2)	
Types of delivery (number) (%)	Vaginal	18 (36)	7 (14)	0.02*
	Cesarean	32 (64)	43 (86)	
Mother uses betamethasone (number) (%)	Yes	42 (85.7)	44 (88)	0.74*
	No	7 (14.3)	6 (12)	
Pregnancy complications	None	28 (56)	25 (50)	0.20*
	Preeclampsia	8 (16)	6 (12)	
	Hypertension	4 (8)	1 (2)	
	Premature rupture of membranes	12 (24)	9 (18)	
	Gestational diabetes mellitus	1 (2)	6 (12)	
Gender (number) (%)	Boy	25 (50)	31 (62)	0.22*
	Girl	25 (50)	19 (38)	
Birth weight (gr) (Mean ± SD)		1575.30 ± 469.12	1627.30 ± 508.0	0.598**

Vitamin D level (ng/mL) (Mean ± SD)	26.76 ± 12.88	26.10 ± 12.02	0.792**
Hospitalization period (day) (Mean ± SD)	18.13 ± 0.56	20.19 ± 11.12	0.53**

* *chi-square*
** *T-Test*

According to the statistical analysis, there was no significant difference in the gender distribution, of the infants between the two groups (P=0.22), indicating that the groups were homogeneous regarding infant gender. Furthermore, there were no significant differences between the intervention and control groups in terms of neonatal prognosis (P=0.43), average length of hospital stays (P=0.53), birth weight (P=0.59), vitamin D levels (P=0.79), and amniotic fluid volume (P=0.63), as shown in Table 2.

Table 2: Infant characteristics in two intervention and control groups.

Variable		Intervention group (n=50)	Control group (n=50)	P-value
Gender N (%)	Boy	25 (50)	31 (62)	0.22*
	Girl	25 (50)	19 (38)	
Prognosis (number) (%)	Death during hospitalization	7 (14)	7 (14)	0.43*
	Hospital discharge	25 (50)	19 (38)	
	Hospital discharge with personal consent	18 (36)	24 (48)	

* *chi-square*
** *T-Test*

An examination of clinical symptoms revealed that most infants exhibited respiratory distress, with 49 (98%) in the intervention group and all 50 (100%) in the control group. There was no significant difference in the incidence of respiratory distress between the two groups (P=0.50). Table 3 displays the frequency distributions of the primary symptoms of respiratory distress in infants.

The frequency of mechanical ventilation in both the intervention and control groups was significantly different (P=0.03). This suggests that the control group of infants received more mechanical ventilation than the intervention group. However, when it comes to the duration of mechanical ventilation, no significant difference was observed between the two groups (P=0.120). No significant difference was observed between the two groups in terms of continuous positive airway pressure (CPAP) (P=0.50), duration of CPAP (P=0.27), high-flow nasal cannula (HFNC) (P=0.09), duration of HFNC (P=0.14), oxygen hood (P=0.55), and duration of oxygen hood (P=0.54).

A significant difference was observed between the intervention and control groups regarding surfactant administration (P=0.009) and the number of times the surfactant was administered (P=0.02). This indicates that the intake of surfactant in the intervention group was significantly less than in the control group.

Table 3: Comparison of Clinical Symptoms in Infants Between Intervention and Control Groups.

Variable		Intervention group (n=50)	Control group (n=50)	P-value
Mechanical ventilation N (%)	Yes	10 (20)	20 (40)	0.03*
	No	40 (80)	30 (60)	
Duration of ventilation (Hour) (Mean ± SD)		25.71 ± 66.59	92.29 ± 58.69	0.120**
Surfactant N (%)	Yes	16 (32)	29 (58)	0.009*
	No	34 (68)	21 (42)	

* *chi-square*
** *T-Test*

Discussion

Based on the results of this study, the administration of 10,000 IU of vitamin D to premature infants reduces respiratory issues, thereby decreasing the need for both initial and advanced respiratory care. Additionally, it decreases the requirement for surfactant administration. To the best of our knowledge, this is the first clinical trial investigating respiratory complications associated with vitamin D administration in neonates. Moreover, the usage frequency of NIV was significantly lower in the intervention group compared to the control group. A recent study conducted by Boskabadi et al. 2019, revealed a significant correlation between the level of vitamin D in infants and the incidence of respiratory distress syndrome and the level of vitamin D in the mother.[9] The findings of this study align with those of the current study, indicating an increased need for respiratory support in premature infants who have a deficiency in vitamin D. In line with the present study, research conducted in China has demonstrated that early intake of vitamin D can significantly decrease the incidence of bronchopulmonary dysplasia in premature infants. Furthermore, this early vitamin D consumption can significantly reduce the serum level of 25(OH)D3. As a result, it prevents bronchopulmonary dysplasia in infants.[15]

Onwuneme et al. demonstrated that preterm infants with low levels of 25-hydroxyvitamin D (less than 30 nmol/L) at birth were associated with an increased need for oxygen, a longer duration of intermittent positive pressure ventilation during labor resuscitation, and a greater requirement for assisted ventilation.[16]

Contrary to this study, Fallahi et al. 2016, found that when comparing groups with vitamin D deficiency and normal levels, there was no difference in the duration of mechanical ventilation between the groups. In other words, both groups had similar durations of mechanical ventilation.[17]

Embryos receive vitamin D solely from their mothers. The amount transferred depends on the mother's exposure to sunlight and vitamin D consumption.[18] During pregnancy, levels of 1,25-hydroxyvitamin D increase during the first trimester and peak in the third trimester, which is twice the levels observed outside of pregnancy. Levels of Vitamin D-binding protein rise in correlation with an increase in the mother's serum vitamin D levels.[19] Having missed this crucial period, premature neonates are at risk of vitamin D deficiency. This is because essential nutrients, including vitamin D, are primarily transmitted during the third trimester of pregnancy.[20] According to Boskabadi et al. 2019, nearly half of all premature infants suffer from severe vitamin D deficiencies.[9] Preterm neonates with vitamin D deficiency were found to be deficient in 89% of cases, respectively, and half of them were severely deficient.[21]

The emerging field of research that focuses on the impact of vitamin D on lung growth and maturation in early life, as well as its influence on lung diseases and respiratory symptoms, is intriguing. Numerous studies suggest that a deficiency in vitamin D may pose a risk factor for respiratory distress syndrome in infants born prematurely. In a similar study, Ataseven et al. 2013, discovered that premature infants with severe vitamin D deficiency are more likely to experience respiratory distress syndrome than those with mild to moderate vitamin D deficiency.[22] Mohamed Hegazy et al. demonstrated that the average concentration of 25-hydroxyvitamin D in the serum of premature infants suffering from respiratory distress syndrome is significantly lower compared to those without the syndrome. Moreover, patients suffering from respiratory distress syndrome who also have low levels of 25-hydroxyvitamin D tend to have longer hospital stays compared to those without the syndrome.[23] Similarly, Yu et al. 2017, have suggested that a deficiency in vitamin D could potentially be linked to an increased risk of respiratory distress syndrome in infants born prematurely. They also discovered that maintaining adequate levels of vitamin D could potentially be beneficial for the maturation of lungs in humans.[24]

Alveolar epithelial-mesenchymal interactions are crucial in perinatal lung development.[25] Premature birth, caused by structural lung immaturity and inadequate surfactant production, is associated with respiratory distress syndrome in humans.[26] In an observational study, Koroglu and colleagues observed increased mechanical ventilation and surfactant treatment among 109 preterm infants deficient in vitamin D.[27] Vitamin D reduces lung injury by stimulating the proliferation and migration of ATII cells, reducing epithelial cell apoptosis, and inhibiting TGF-β-induced Epithelial-Mesenchymal Transition (EMT). Vitamin D treatment significantly reduces inflammatory responses and cellular apoptosis in the lung tissue of mice model asthma, according to Zhang et al.[28] Another study reported that vitamin D has therapeutic potential for acute respiratory distress syndrome.[29]

Boskabadi et al. (2018) conducted a case-control study on 160 preterm infants to assess the relationship between vitamin D levels and respiratory distress.[30] Their research, conducted in Mashhad, Iran, revealed that infants with respiratory distress had significantly lower maternal and neonatal vitamin D levels than those without respiratory distress. Factors such as duration of hospitalization, gestational age, birth weight, Apgar scores, and head circumference were associated with neonatal vitamin D levels. Complications, including death and pneumothorax, were observed among infants with respiratory distress. These findings highlight the potential protective role of adequate vitamin D levels against respiratory distress in preterm infants, underscoring the importance of further research and interventions to optimize neonatal health outcomes.

Additionally, Boskabadi et al. (2020) conducted a case-control study to investigate the association between serum vitamin D levels and transient tachypnea of the newborn (TTN), a common cause of respiratory distress in neonates.[31] The research carried out from 2016 to 2019 in a general hospital affiliated with Mashhad University of Medical Sciences, Iran, included 34 infants with TTN and 82 neonates in the control group, along with their mothers. The study found that infants with TTN and their mothers had significantly lower serum vitamin D levels than the control group. Specifically, the mean differences in neonatal and maternal vitamin D levels between the two groups were 11.10 ng/mL and 13.36 ng/mL, respectively. Additionally, all infants in the TTN group had vitamin D levels below 30 ng/mL, with the majority exhibiting severe deficiency, highlighting the potential importance of addressing maternal vitamin D deficiency in reducing the incidence of TTN in newborns.

Moreover, Pourbadakhshan et al. (2023) conducted a single-blind clinical trial to assess the impact of administering 50,000 units of 25-hydroxy vitamin D to pregnant women at risk of preterm delivery on the incidence of non-specific respiratory distress syndrome (NRDS) in their newborns.[32] The study, conducted from February 20, 2021, to June 29, 2021, at Ghaem Hospital, affiliated with Mashhad University of Medical Sciences, Iran, included mothers and neonates with a gestational age of 32–37 weeks. Results showed a significant difference between the intervention and control groups regarding infant weight, 1-minute and 5-minute Apgar scores, and the incidence of NRDS. However, there were no significant differences between the groups regarding gender, type of delivery, and levels of 25-hydroxy vitamin D in the mother and infant. The findings suggest that a single vitamin D injection in pregnant women at risk of preterm birth reduces transient respiratory problems in their newborns.

One limitation of this study is the lack of vitamin D level testing after injection. In addition, premature babies are more susceptible to different problems simultaneously, which affects the accurate identification of patients with respiratory problems. More studies should be conducted on a larger population of preterm infants to evaluate the relationship between maternal and infant vitamin D status. Future studies should examine the adaptation of newborns to mothers' vitamin D levels.

Conclusion

Based on the results obtained from this study, vitamin D consumption at birth is effective in the prognosis of premature infants. It reduces the need for NIV, mechanical ventilation, and surfactant. Generally, vitamin D consumption at birth reduces the incidence of respiratory complications in premature infants.

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