Alicja Kołodziejczyk, Maria Katarzyna Borszewska-Kornacka

MONITORED SUPPLEMENTATION OF VITAMIN D IN PRETERM NEONATES – A PRIMARY REPORT

MONITOROWANA SUPLEMENTACJA WITAMINY D U NOWORODKÓW URODZONYCH PRZEDWCZEŚNIE – DONIESIENIE PIERWSZE

Department of Neonatology and Neonatal Intensive Care, Medical University of Warsaw, Poland

Abstract

Aim: *To evaluate vitamin D (vitD) monitored therapy effectiveness and safety in preterm neonates.*

Patients and methods: *Our observational study was carried out in 80 neonates born before 33 weeks' gestational age (GA) hospitalized in the Clinical Department of Neonatology and Neonatal and Intensive Care Department Medical University of Warsaw from July 2013 to July 2014. Daily vitamin D oral supplementation was provided from 1 to 3 weeks of age at the dose of 500-1000 IU/24 h. The dosage was modified according of 25-hydroxyvitamin-D blood serum concentration. Both blood serum 25(OH) D concentration and calcium-phosphate metabolism were assessed at 4 weeks of age, at 34-37 weeks' post-conceptual age (on discharge) and at 39-41 weeks PCA.*

Results: *Mean serum 25(OH)D level was 40 ng/ml at 4 weeks of age, 61 ng/ml at 34-37 weeks PCA, and 53 ng/ml at 39-41 weeks PCA. Higher concentrations were observed in ELBW neonates. Deficiency was noted most often at the first measurement. 52.5% of neonates received 500IU vitD before discharge, 19% had stopped supplementation due to overdosing. High dose vitD supplementation was provided in 34% cases. Disturbance of calcium-phosphate metabolism due to vitD deficiency was observed in one patient. Hypervitaminosis was associated with higher calcium-creatinine ratio. Very high individual heterogeneity of 25(OH)D concentration changes were observed (from 70 ng/ml/4 weeks decrease to 92 ng/ml/4 weeks increase).*

Conclusions: *Supplementation of vitamin D in preterm neonates needs monitoring. A safe time interval to monitor vitamin D supplementation seems to be 1 month. The schedule of the therapy requires further studies.*

Key words: preterm infants, premature neonates, vitamin D supplementation, 25-hydroxyvitamin D, calcium-phosphate metabolism

Streszczenie

Cel: *Ocena bezpieczeństwa oraz efektywności monitorowanej suplementacji witaminy D u noworodków urodzonych przedwcześnie.*

Materiał i metody: *Badanie obserwacyjne przeprowadzono na 80 noworodkach urodzonych przed 33 tygodniem wieku ciążowego hospitalizowanych w Klinice Neonatologii i Intensywnej Terapii Noworodka Warszawskiego Uniwersytetu Medycznego w okresie od lipca 2013 roku do lipca 2014. Witaminę D podawano doustnie od 1-3 tygodnia życia w dawce 500-1000 IU/dobę. Dawkowanie modyfikowano w zależności od stężenia 25-hydroksywitaminy D w surowicy krwi. Stężenie 25(OH)D oraz gospodarkę wapniowo-fosforanową oznaczano w 4 tygodniu życia, w 34-37 tygodniu wieku postkoncepcyjnego oraz w 39-41 tygodniu wieku postkoncepcyjnego.*

Wyniki: *Średnie stężenie 25(OH)D w pomiarze w 4 tygodniu życia wynosiło 40 ng/ml, 61ng/ml w 34-37 tygodniu wieku postkoncepcyjnego oraz 53 ng/ml w 39-34 tygodniu wieku postkoncepcyjnego. Wyższe stężenia obserwowano w grupie noworodków z ekstremalnie mała masą ciała. Niedobór zaobserwowano najczęściej podczas pierwszego pomiaru. 52,5% noworodków otrzymywało przed wypisem suplementację 500IU, 19% noworodków wymagało zaprzestania suplementacji w wyniku przedawkowania. Suplementację witaminy D wysokimi dawkami prowadzono u 34% pacjentów.*

W wyniku niedoboru witaminy D zaburzenia gospodarki wapniowo-fosforanowej były obserwowane u jednego noworodka. Hiperwitaminoza witaminy D wiązała się z podwyższeniem wskaźnika wapniowo-kreatyninowego. Obserwowano dużą różnorodność osobniczą w zmianie stężenia 25(OH)D (od spadku 70 ng/ml/4 tygodnie do wzrostu 92 ng/ml/4 tygodnie).

Wnioski: *Suplementacja witaminy wymaga monitorowania. Bezpiecznym przedziałem czasowym monitorowania terapii u noworodków urodzonych przedwcześnie jest miesiąc. Schemat prowadzenia powyższej terapii wymaga dalszych badań.*

Słowakluczowe: *noworodki urodzone przedwcześnie, suplementacja witaminy D, 25-hydroksywitamina D, gospodarka wapniowo-fosforanowa*

DEV PERIOD MED. 2015;XIX,3,CZ.I:313-318

INTRODUCTION

Deficiency of vit D is a risk factor of the osteopenia of prematurity, which leads to rickets or lowers both bone mass and bone mineral density [1, 20, 21]. The second effect of the lack of vitD in infancy is a higher frequency of respiratory tract infections [22]. Appreciable deficiency can lead to seizures, lethargy and growth disturbance [4, 7]. Some authors identify deficiency of vitD during pregnancy as a risk factor of preterm birth [8, 11] and language impairment among offspring [5, 23]. More and more studies document the improvement of the immune system during proper supplementation of vitD and the reduction of cardiovascular, neoplastic and musculoskeletal diseases [15]. Overdosage of vitD, however, can lead to hypercalcuria and nephrolithiasis [7].

The dosage, safety and effectiveness of vitD supplementation in preterm neonates is a controversial topic. According to the recommendations for Central Europe, preterm neonates should receive supplementation from the first days of life (when enteral feeding is possible) in the dose 400-800 IU/day till 40 weeks of gestational age, then 400 IU/day [16], whereas according to the guidelines of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, the supplementation of vitD for premature neonates should reach 800-1000 IU/day [2, 10]. Also, the dosage of 200-400IU/day for preterm neonates can be found in experts' recommendations [12, 13, 17, 18].

PATIENTS AND METHODS

Our study was carried out in the Clinical Department of Neonatology and Neonatal and Intensive Care Department the Medical University of Warsaw from July 2013 to July 2014. 80 neonates born before 33 weeks GA were enrolled in the study. 26% of the neonates were extremely low birth weight (ELBW) infants, the average gestational age was 29 weeks. Most of the neonates during hospitalization were fed fortified human milk. The demographic characteristic of the neonates is shown in table II. The eligibility criteria of the study included: gestational age below 33 weeks, measurement of both 25(OH)D concentration and calcium-phosphate metabolism at 4 weeks of age and at 34-37 weeks' PCA. In 31 cases, the measurement in the 4 th week of age coincided with the measurement at 34-37 weeks' PCA. In 52 cases, 25(OH)D concentration and calcium-phosphate metabolism were additionally tested in our outpatient clinic during the visit at 39-41 weeks' PCA. In 16 cases, additional measure during hospitalization, between the first measurement and on discharge, was taken.

During the hospitalization vitD was supplemented by preparation: Devicap 15 000 IU/ml. The oral supplementation 500 IU or 1000 IU was started after the stop of lipid supplementation in parenteral feeding (1^{st}-3^{rd} week of life). Parenteral feeding contains 160 IU/kg of vitD (Vitalipid). Additional supplementation of vitD comes from: human milk (2-5 IU/kg), fortified human milk (160 IU/kg), preterm formula (190 IU/kg) and transitional formula (190 IU/kg). The 25(OH)D concentration target ranged from 30 to 80 ng/ml. Dose modification was carried out based on the results of measurement, the experience and knowledge of doctors. From the period between the discharge and the visit in the outpatient clinic, neonates were being supplemented over-the-counter preparation (dose 400 IU or its multiple) or the supplementation ceased.

The level of vitD was assayed in a hospital laboratory by immunoenzymatic technique ELFA (VIDAS 25 OH Vitamin D Total), requiring 200 ul serum. Calcium-phosphate metabolism was assayed by the kinetic method, requiring 150 ul blood serum and 200 ul urine.

RESULTS

Mean blood serum 25(OH)D concentration was: 40 ng/ml at 4 week of age, 61 ng/ml at 34-37 weeks' PCA, and 53 ng/ml at 39-42 weeks' PCA. Higher concentration at 34-37 weeks' PCA was observed in extremely low birth weight neonates (76 ng/ml vs 61 ng/ml). Due to the higher dose per kilo, in ELBW neonates group vitD was more frequently overdosed – 24% vs 13%. Deficiency of vitD was predominately observed during the first measurement-9% of neonates. The normal range, in all measurements, was achieved in 71% of all the neonates and 62% of ELBW neonates. 25(OH)D blood serum concentration distribution in neonates is shown in figure 1.

Table I. References values [3, 7, 15].

Tabela I. Wartości referencyjne [3, 7, 15].

Parameters/*Parametry*	**Value** ***Wartość***	**Reference values** ***Wartości referencyjne***
25(OH)D	<20 ng/ml (<50 nmol/l)	deficiency *niedobór*
	20-30 ng/ml (50-75 nmol/l)	suboptimal level *stężenie suboptymalne*
	30-50 ng/ml (75-125 nmol/l)	optimal level *stężenie optymalne*
	50-100 ng/ml (125-250 nmol/l)	high level *stężenie wysokie*
	>100 ng/ml (>250 nmol/l)	potentially toxic level *stężenie potencjalnie toksyczne*
	>200 ng/ml (>500 nmol/l)	toxic level *stężenie toksyczne*
ALP	>900I/U	elevated *podwyższona*
Serum calcium *Wapń w surowicy*	2.25-2.65 mmol/l	norm *norma*
Serum phosphate *Fosfor w surowicy*	5.5-8.7 mg/dl	norm *norma*
Ca/creatinine ratio *Wsk. wapniowo-kreatyninowy*	<0.8 mg/mg	norm *norma*
P/creatinine ratio *Wsk. fosforanowo-kreatyninowy*	0.34-5.24 mg/mg	norm *norma*

Table II. Demographic characteristics.

Tabela II. Charakterystyka demograficzna.

n neonates *liczba noworodki*	80	
n (%) female *liczba (%) płeć żeńska*	29	(36.3%)
n (%) ELBW *liczba (%) ELBW*	21	**(26.3%)**
n (%) neonates born<29GA *liczba(%) noworodki <29 tyg. wieku ciążowego*	28	(35%)
n (%) hypertrophy *liczba (%) hypertrofia*	19	**(23.8%)**
Average birth weight [range] *Średnia masa ciała [przedział]*	1284 g	[570-2175 g]
Average GA in weeks [range] *Średni wiek ciążowy [przedział]*	29GA	[24-32GA]
n (%) parenteral nutrition ≥14 days *liczba (%) żywienie parenteralne ≥14 dni*	35	(43.8%)
n (%) human milk + fortifier *liczba (%) pokarm kobiecy +wzmacniacz*	74	**(92.5%)**

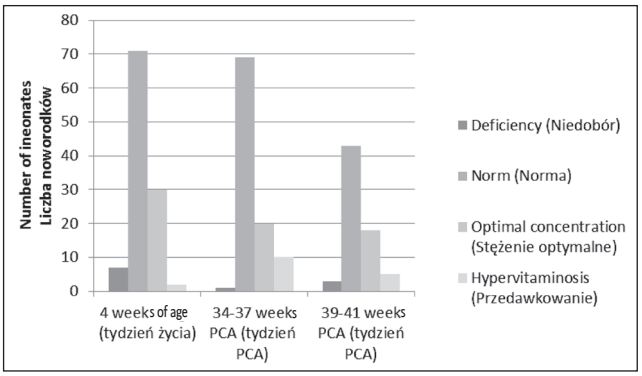

Fig. 1. 25(OH)D serum level in neonates.

Ryc. 1. Stężenie 25(OH)D w surowicy u noworodków.

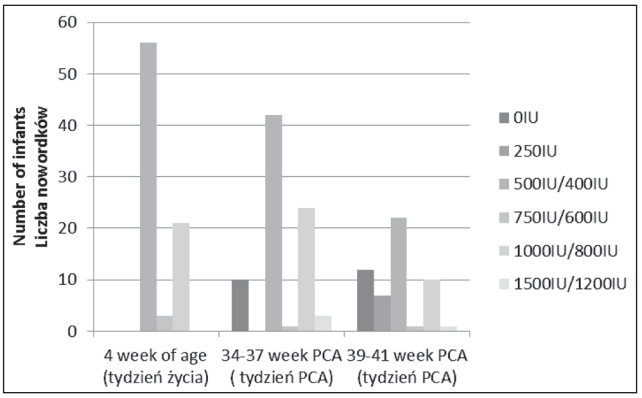

Fig. 2. Supplementation of vitamin D.

Ryc. 2. Suplementacja witaminy D.

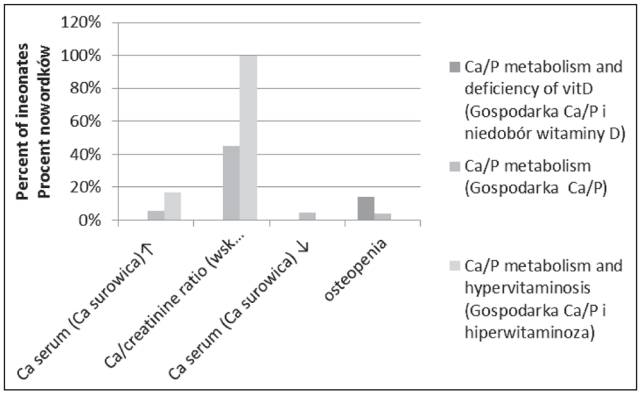

Fig. 3. Calcium-phosphate metabolism disturbance and vitamin D intake.

Ryc. 3. Zaburzenia gospodarki wapniowo-fosforanowej a witamina D.

The initial dose which was most frequently adopted was 500 IU/day (in 70% cases). The pre-discharge dose was modified based on blood serum 25(OH)D concentration measurement. Slightly more than half the neonates received 500 IU vitD before the discharge. 19% of the neonates had stopped the supplementation due to overdosing. Based on the results, a high dose (1000-1500 IU)of vitD supplementation was provided to 34% of the patients. The supplementation dose distribution is shown in figure 2.

Alkaline phosphate increase was identified in 7% of the neonates (based on calcium-phosphate metabolism at 4 weeks of age and at 34-37 weeks PCA). 3.8% of the neonates had both alkaline phosphate increase and serum phosphorus decrease, which is the most specific and sensitive biochemical parameter of preterm osteopenia [3]. About half of the neonates were observed to have increased creatinine-calcium ratio. One patient was tested to have disturbance of calcium-phosphate metabolism due to vitD deficiency. Throughout the study, hypervitaminosis was coinciding with a higher calcium-creatinine ratio (fig. 3).

Based on the results, neonates with hypervitaminosis at 34-37 weeks PCA (13% of neonates) could be divided into two groups. In the first group (6 cases) mean serum 25(OH)D concentration at 4 weeks of age was at the upper normal range and despite earlier discontinuance of oral supplementation, serum 25(OH)D concentration was still above normal range. In the second group (4 cases), hypervitaminosis was observed due to the increase or continuation of high dose supplementation (1000 IU) in the treatment of vitamin D deficiency (diagnosed in the first measurement).

Suboptimal 25(OH)D concentration or 25(OH)D deficiency at 34-37 weeks PCA was noted in 19% of the neonates. Despite supplementation, or even high dose supplementation, a serum 25(OH)D concentration decrease was observed within this group (53%).

The most frequently noted time between the subsequent measurement was 2 or 4 weeks.

After 2 weeks of discontinuation of vitD supplementation, a serum 25(OH)D concentration decrease was not observed. The maximum decrease amounted to 30 ng/ml per 2 weeks. Despite discontinuation of vitD supplementation in one group of neonates, a serum 25(OH)D concentration increase was noted, maximum 21 ng/ml per 2 weeks. It is a result of additional vitamin D supplementation in the fortifier and milk formula or 25(OH)D half-life in organism. Mean increase of vitD during 500IU supplementation was 7.5ng/ml per 2 weeks and during 1000 IU – 29ng. A decrease of 25(OH)D despite supplementation was observed in 4 cases. The maximum increase was 78ng/ml per 2 weeks. The changes of 25(OH)D concentration during 2 weeks of supplementation at different doses are shown in figure 4.

In a four-week period between the subsequent measurements during the discontinuation of supplementation, the average 25(OH)D decrease amounted to 31.5 ng/ml per 4 weeks. Even in all the cases where a decrease was observed, the maximum decrease was 70 ng/ml per 4 weeks. The mean serum 25(OH)D increase during 500 IU supplementation amounted to 11 ng/ml per 4 weeks, which means the tendency of 25(OH)D stabilization was observed. Large individual heterogeneity was identified. Decrease as well as increase were observed. The maximum decrease was 19 ng/ml per 4 weeks, the maximum increase 72 ng. During 1000 IU supplementation, a further mean 25(OH)D increase (38 ng/ml per 4 weeks) was observed. Large individual heterogeneity was also

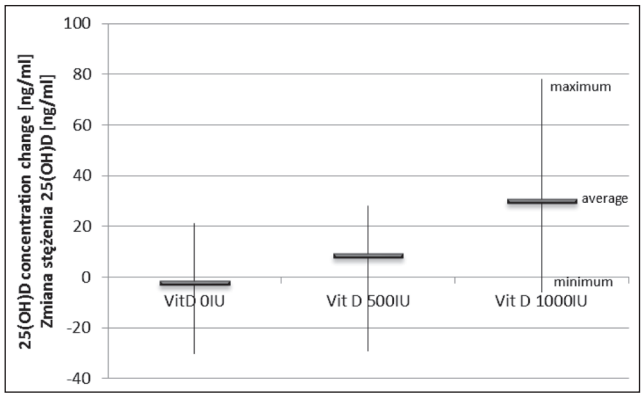

Fig. 4. Change of 25(OH)D concentration after 2 weeks of supplementation at different doses.

Ryc. 4. Zmiana stężenia 25 (OH)D po 2 tygodniach suplementacji w zależności od dawki.

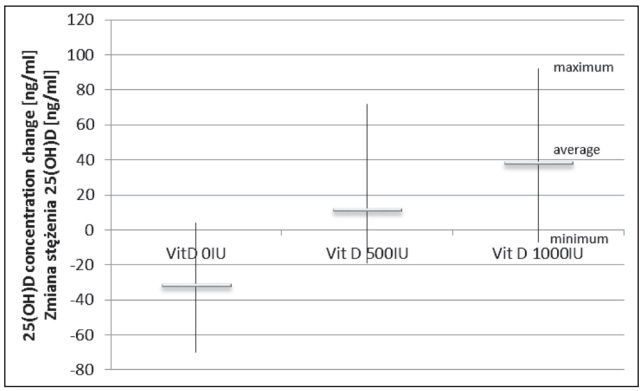

Fig. 5. Change of vitamin D concentration after 4 weeks of supplementation at different doses.

Ryc. 5. Zmiana stężenia 25 (OH)D po 4 tygodniach suplementacji w zależności od dawki.

detected. The maximum decrease was 7 ng/ml per 4 weeks and the increase 92 IU. The changes of 25(OH) D concentration during 4 weeks of supplementation at different doses are shown in figure 5.

DISCUSSION

Preterm neonates comprise a very heterogeneous group of patients. According to the literature, the level of metabolite of vitD at birth is strongly correlated with maternal vitD statute and oscillates in the large interval. Both assimilation and metabolism of vitD in preterm neonates seem to differ from term neonates. Furthermore, supplementation of vitD per kilo of weight varies significantly.

To date, there have been no recommendable serum 25(OH)D concentration norms for neonates addressed in the guidelines for Central Europe [16]. According to these recommendations: <20 ng/ml occurs deficit, 20-30 ng/ml is the suboptimal concentration and the dosage should be mildly increased; 30-50 ng/ml is the optimal concentration, which provides multidirectional action of vitD, and the dose should be continued. 50-100 ng/ml is a high level, the dosage should be decreased if the concentration is in the upper range. Concentration exceeding 100ng/ml is potentially toxic, vitD supplementation should be discontinued until normalization. In the research, osteopenia due to vitD deficiency was observed in one case. Hipercalcuria due to vitD over-dosage was observed in all cases. About half of the neonates were observed to have increased creatinine-calcium ratio which predisposes to an nephrolithiasis. The normal range of vitD is based on recent studies in children, adolescents and adults evaluating intestinal calcium absorption, PTH concentrations and bone density [19]. Separating the norms for preterm neonates proves to be a difficult task, demanding a multi-centre trial.

Preterm neonates are remarkably exposed to vitD deficiency at birth. In the research, vitD was not estimated at birth, which is a vulnerable point of the study, which makes the assumption according to the recommendation that preterm infants need higher dose supplementation. Initially 500 IU-1000 IU vitD was supplemented. A factor in additional supplementation, from fortifier and modified milk initial supplementation, amount to 650-1400 IU/day , whereas supplementation according to the recommendations for Central Europe should amount to 400-800 IU/day. Having applied a higher dose at the first measurement there was no over-dosage, even if there was deficiency in 6 cases. Cases of over-dosage were identified in the measurement at 34-37 weeks PCA. Supplementation should be decreased after the first measurement, when a high 25(OH)D level is achieved and should always be monitored on discharge. The vitD half-life ranges from 4 to 6 weeks. A safe range to monitor vitD supplementation for preterm neonates appears to be 1 month. The reduction of range to 2 weeks is probably aimless due to the amount of blood required for the measurement and the risk of neonatal anemia. The initial dose of 1000 IU can lead to overdosing, whereas the high dose should be reserved when the standard dose is insufficient. The VitD supplementation schedule among preterm neonates is not well established. To date, research which compares results of different supplementation models with no dosage modification has been published [9, 11, 14]. Abrams in Pediatrics (2013) Taylor, Wagner and behind them Mimouni in Neoreviews (2009, 2014) suggest monitoring 25(OH)D concentrations of preterm neonates.

CONCLUSIONS

Supplementation of vitamin D in preterm neonates needs monitoring. A safe time interval to monitor vitamin D supplementation seems to be 1 month. The schedule of the therapy requires further studies.

REFERENCES

1. Abrams SA. In utero physiology: role in nutrient delivery and fetal development for calcium, phosphorus, and vitamin D. Am J Clin Nutr. 2007;85(2):604-607.
2. Agostoni C, Buonocore G, Carnielli VP, et al. ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society

of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85-91.
3. Backström MC, Kouri T, Kuusela A-L, Kuusela AL, Sievänen H, Koivisto AM, Ikonen RS, Mäki M. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. Acta Paediatr. 2000;89(7):867-873.
4. Bhatia J, Griffin I, Anderson D, Kler N, Domellöf M. Selected Macro/Micronutrient Needs of the Routine Preterm Infant. The Journal of Pediatrics. J Pediatr. 2013;162(3):48-55.
5. Czech-Kowalska J, Gruszfeld D, Jaworski M at al. Determinants of postpartum vitamin D status in the Caucasian mother-offspring pairs at latitude. Research grant of Nutricia Foundation No. RG 3/2010
6. Demay MB, Sabbagh Y, Carpenter TO. Calcium and vitamin D: what is known about the effects on growing bone. Pediatrics. 2007;119(2):141-144.
7. Dobrzańska A, Czech-Kowalska J at al. Zaburzenia gospodarki wapniowo-fosforanowej-osteopenia wcześniaków. Leksykon 2008;57-65.
8. Dziadosz M, Parisi V, Warren W, Miller R. Vitamin D deficiency in early gestation and rates of preterm birth: a retrospective cohort study. American Journal of Obstetrics and Gynecology. 2014;210(1):391.
9. Fort P, Salas AA et al. Randomised clinical trial of vitamin d supplementation in extremely preterm infants. Journal of investigative Medicine 2015;63:2 (417).
10. Grant CC, Stewart AW, Scragg R, Milne T, et al. Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration. Pediatrics. 2014;133(1):143-153.
11. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner Cl, et al. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res. 2011;26(10):2341-2357.
12. McCarthy RA, McKenna MJ, Oyefeso O, et al. Vitamin D nutritional status in preterm infants and response to supplementation. Br J Nutr. 2014;110(1):156-163.
13. Monangi N, Slaughter J, Dawodu A, et al. Vitamin D status of early preterm infants and the effects of vitamin D intake during hospital stay. Arch Dis Child Fetal Neonatal Ed. 2014;99:166-168.
14. Natarajan CK, Sankar MJ, Agarwal R et al. Trial of daily vitamin D supplementation in preterm infants. Pediatrics. 133(3):e628-34. doi: 10.1542/peds.2012-3395.
15. Pludowski P, Holick MF, Pilz S at al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality- A review of recent evidence. Autoimmun Rev. 2013;12:976-989.
16. Płudowski P, Karczmarewicz E, Bayer M, Carter G at al. Practical guidelines for the supplementation of vitamin D and the treatment of deficit in Central Europe-recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol. 2013;64:319-327.
17. Rigo J, Pieltain C, Salle B, Senterre J et al. Enteral calcium, phosphate and vitamin D requirements and bone mineralization in preterm infants. Acta Paediatr. 2007;96(7):969-974.
18. Steven A. Abrams and the Commitee on Nutrition (2013) Calcium and Vitamin D Requirements of Enterally Fed Preterm Infants. Pediatrics. 131(5):1676-1683.
19. Taylor SN, Hollis BW, Wagner CL. Vitamin D Needs of Preterm Infants NeoReviews 2009;10;e590.
20. Tsang RC, Uauy R, Koletzko B, Zlotkin SH. Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines. 2nd Edition Digital Educational Publishing 2005 ISBN-13: 978-1583521007.
21. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics. 2008;122(5):1142-1152.
22. Walker VP, Modlin RL. The vitamin D connection to pediatric infections and immune function. Pediatr Res. 2009;65(5):106-113.
23. 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;129(3):485-493.

Abbreviations:
25(OH)D – 25-hydroxyvitamin D
ELBW – extremely low birth weight
PCA – post-conceptual age
GA – gestational age
vitD – vitamin D

Author's contributions/Wkład Autorów
According to the order of the Authorship/Według kolejności

Conflicts of interest/Konflikt interesu
The Authors declare no conflict of interest.
Autorzy pracy nie zgłaszają konfliktu interesów.

Received/Nadesłano: 12.05.2015 r.
Accepted/Zaakceptowano: 07.08.2015 r.

Published online/Dostępne online

Address for correspondence:
Alicja Kołodziejczyk
Department of Neonatology
and Neonatal Intensive Care,
Medical University of Warsaw Poland
2 Karowa Street, 00-315 Warsaw
tel.: (+48 22) 59-66-155, (+48) 501-049-246
fax: (+48 22) 59-66-484
e-mail: alicja.kolodziejczyk@wum.edu.pl