Neuroendocrinology Letters
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Effects of maternal vitamin D status on pregnancy outcomes, health of pregnant women and their offspring

Elżbieta Skowrońska-Jóźwiak [1], Katarzyna Lebiedzińska [2], Joanna Smyczyńska [1], Krzysztof C. Lewandowski [1], Ewa Głowacka [3], Andrzej Lewiński [1]

1 Department of Endocrinology and Metabolic Diseases Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland
2 Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland
3 Department of Laboratory Diagnostics Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland

Correspondence to: Prof. Andrzej Lewiński
Department of Endocrinology and Metabolic Diseases,
Polish Mother's Memorial Hospital – Research Institute,
Rzgowska St. No. 281/289, 93-338 Lodz, Poland.
E-MAIL: alewin@csk.umed.lodz.pl

Submitted: 2014-08-02 *Accepted: 2014-08-28* *Published online: 2014-09-28*

Key words: **vitamin D; pregnancy; bacterial vaginosis**

Neuroendocrinol Lett 2014; **35**(5):367–372 **PMID:** 25275261 NEL350514A07 ©2014 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVE: Pregnancy increases the demand for vitamins, including vitamin D. Data on effects of vitamin D deficiency for pregnant woman and fetus available in Poland are scarce. The aim of this study was to evaluate vitamin D3 concentration in pregnant women and its influence on pregnancy course, health of pregnant women and their offspring.

PATIENTS AND METHODS: The study included 102 healthy pregnant women, aged 21 to 40 years, mean 30.5±4.9 years. Women were divided into three groups based on 25(OH)D serum concentration in the third trimester of pregnancy: Group I – with sufficient 25(OH)D serum concentration (>30 ng/ml), Group II – with vitamin D3 insufficiency (20–30 ng/ml), Group III – with serious vitamin D deficiency (<20 ng/ml).

RESULTS: Optimal vitamin D concentrations were found only in 31.2% of women, however in winter months only in 16%. Bacterial vaginosis was significantly more common in women with vitamin D deficiency and insufficiency ($p<0.05$). In contrast, there were no relations between vitamin D status and the incidence of gestational diabetes, preeclampsia, mode of delivery and size of newborns. A relationship between vitamin D deficiency and insufficiency during pregnancy and subsequent incidence of respiratory infections in children ($p<0.05$) was demonstrated.

CONCLUSIONS: 1. The current model of vitamin D supplementation in pregnant women in Poland is insufficient, particularly in winter. 2. Vitamin D deficiency in pregnant women fosters development of bacterial vaginosis during pregnancy and recurrent respiratory infections in children, suggestive of the role of vitamin D in prevention of infections.

O R I G I N A L A R T I C L E

INTRODUCTION

Pregnancy increases the demand for vitamins and microelements, including vitamin D. Adaptation of calcium metabolism to pregnancy involves doubling of calcitriol synthesis that necessitates an adequate supply of vitamin D (Kovacs & Kronenberg 1997). While only less than 10% of vitamin D is derived from dietary sources, skin synthesis, requiring ultraviolet (UV) radiation, remains the main source of vitamin D (Holick 2009). Unfortunately, in Poland UV availability is sufficient only from May to September (Płudowski *et al.* 2013). On the other hand, UV is regarded as the major environmental, physical hazard to the human skin (Osmola-Mańkowska *et al.* 2012). Furthermore, the amount of vitamin D in most multivitamin supplements designed for pregnant women is not sufficient, while not all pregnant women declare taking those supplements (Bojar *et al.* 2012; Skowrońska-Jóźwiak *et al.* 2014).

Vitamin D takes part in reproduction processes and seems to be significant in therapy of infertility (Grzechocinska *et al.* 2013). Maternal vitamin D deficiency during pregnancy may be associated with adverse pregnancy outcomes, such as miscarriage, preeclampsia (Bodnar *et al.* 2007), preterm birth (Møller *et al.* 2012), gestational diabetes (Senti *et al.* 2012) and bacterial vaginosis (Bodnar *et al.* 2009). Vitamin D deficiency during pregnancy may affect child's health, because maternal circulating 25(OH)D is the most significant regulator of neonatal circulating 25(OH)D concentrations and predominates over genetic factors that determine neonatal circulating vitamin D concentrations (Novakovic *et al.* 2012). Offspring of vitamin D-deficient mothers are at risk of not only classical bone complications such as rickets, low bone mineral density and the reduced postnatal linear growth (Pawley & Bishop 2004), but also of respiratory infections and asthma (Camargo *et al.* 2011), diabetes type 1 (Hypponen *et al.* 2001) and schizophrenia (McGrath *et al.* 2004) later in life. Data available in Poland on the effects of vitamin D deficiency in pregnant women are very scarce.

The aim of this study was to evaluate seasonal variation of vitamin D3 concentrations and a relationship between vitamin D3 status in pregnant women and pregnancy outcomes, health of pregnant women and their children.

Tab. 1. Characteristics of the study group.

	Mean±SD
Age [years]	31.4±4.2
Height [cm]	165±6
Body mass [kg]	69.6±15.2
BMI [kg/m^2]	25.4±5.1

PATIENTS AND METHODS

The study included 102 healthy pregnant women, of aged between 21 to 40 years, mean age 30.5±4.9 years, investigated in the third trimester of gestation. The majority of women (64%) declared taking vitamin supplements and most of them were taking 400IU of vitamin D daily. The women were subsequently divided into three groups: those with sufficient serum vitamin D3 – above 30 ng/ml (Group I), with vitamin D3 insufficiency, defined as the concentration of 25(OH) D in the range of 20–30 ng/ml (Group II) and vitamin D deficiency – less than 20 ng/ml (Group III), according to definition based on Endocrine Society's Practice Guidelines on Vitamin D (Holick *et al.* 2011). Concentrations of 25(OH)D were determined by electrochemiluminescence assay (Elecys, Roche). Characteristics of investigated subjects is presented in Table 1.

In statistical analysis the standard descriptive statistics were used, including the typical measures of the distribution characteristics of the population – the mean value, standard deviation (SD). Assessment of differences between more than two groups of patients, in which distribution of the most variables did not meet the criteria of normal distribution, was performed with non-parametric Kruskall-Wallis test, followed by the post-hoc analysis for multiple bilateral comparisons in order to identify significant differences between particular groups. The distribution of qualitative variables in particular groups was presented in cross tabulations. Significance of the differences between the distributions of the analysed qualitative variables among particular groups was assessed with Chi-square test. For all the performed tests, the differences were considered significant for $p<0.05$.

The design of study was approved by the Ethics Committee of Medical University at Lodz.

RESULTS

Complete medical data and questionnaire on the course of pregnancy, mode of delivery, health of pregnant women and their offspring were completed for 69 women. There were 42 physiological labours and 27 caesarean sections. Indications for cesarean delivery included: fetal distress (n=6); maternal disparity (n=2); breech presentation (n=3); previous Caesarean section delivery (i.e. risk of scar dehiscence) (n=3); lack of progress of labour (n=4), while maternal indications (n=9) included severe short-sightedness, perivaginal warts and dehiscence of the pubic symphysis.

Optimal vitamin D concentrations was found only in 31.2% of women, however the results depended on the season, in winter recommended vitamin D concentrations was found only in 16% of women and in summer – in 47%. Severe vitamin D deficiency was shown in 23–58% and hypovitaminosis D in 26–37% of pregnant women depending on the season (Figure 1). The

Copyright © 2014 Neuroendocrinology Letters ISSN 0172–780X • www.nel.edu

highest concentration of vitamin D was found in IIIrd quarter, the lowest in IVth quarter of the year (p=0.018) (Figure 2). Monthly fluctuations of vitamin D concentration are presented in Figure 3. Incidence of bacterial vaginosis was significantly higher in women with vitamin D deficiency in comparison to women with optimal vitamin D concentrations (p=0.041). There was also a significant difference between incidence of bacterial vaginosis in women with vitamin D insufficiency versus those with optimal vitamin D concentrations (p=0.002). There was, however, no significant difference in the incidence of bacterial vaginosis between women with vitamin D deficiency and insufficiency (p=0.517) – (Figure 4). There was no relationship between vitamin D levels and the incidence of gestational diabetes and preeclampsia. There was also no statistically significant relationship between maternal vitamin D3 concentrations and the mode of delivery (p=0.80). Maternal concentration of vitamin D were also unrelated to the size of newborns – Table 2. There was a trend towards higher Apgar score in children of mothers with normal levels of vitamin D (Group I), but this failed to reach statistical significance (p=0.2). There was, however, a higher incidence of respiratory infections (more than 5 times per year) during the first year of life among children of mothers from Group III. Significant differences in incidence of recurrent infections in children were observed between the group of children born by mothers with vitamin D deficiency and with optimal vitamin D concentrations (p=0.003), as well as between children of mothers with vitamin D insufficiency and those with optimal vitamin D concentrations (p=0.040). There was no difference in the incidence of recurrent respiratory infections between children of mothers with vitamin D deficiency (Group II) and insufficiency (Group III) (p=0.200) – Figure 5.

DISCUSSION

Our study demonstrated both insufficiency and seasonal variation of vitamin D levels in pregnant women in Poland. The lowest values were found in the fourth quarter of the year (months October–December), where only 16% of women had optimal levels of vitamin D. Significantly higher values were observed in third quarter, responding to summer – when almost half (47%) subjects had recommended vitamin D levels, i.e. above 30 ng/ml. This dependence is associated with fluctuations in skin synthesis of vitamin D and less exposure to sunlight in autumn and winter in Poland (Płudowski *et al.* 2013). Similar data on annual fluctuations in vitamin D levels were reported in Poland at the end of eighties XX century, but in that study vitamin D deficiency was even more serious; i.e. in winter mean concentrations of serum 25(OH)D were only 5.5 ng/ml in mothers and even 3.3 ng/ml in their offspring. In summer results were better – 28.8 ng/ml in mothers and 22.1 ng/ml in children (Pluta *et al.* 1987).

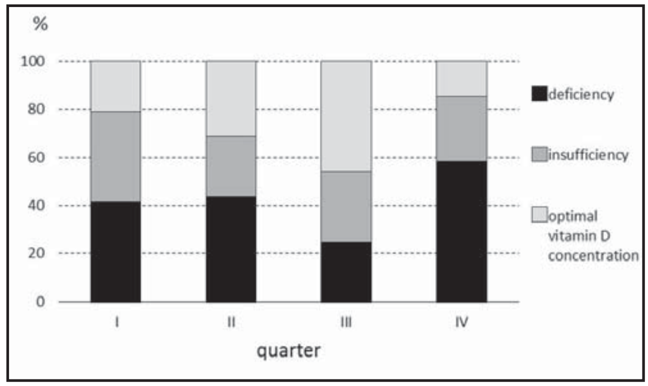

Fig 1. Vitamin D concentration in quarters of a year I–IV, where quarter I indicates a period of January–March, quarter II: April till June, quarter III: July–September, quarter IV: October – December; percentage of pregnant women with optimal vitamin D levels, with vitamin D insufficiency and deficiency was shown.

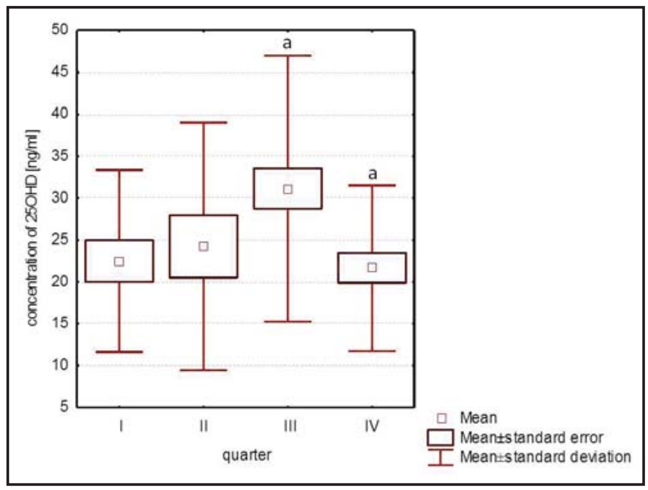

Fig. 2. Mean vitamin D concentrations in quarters I–IV, where quarter I indicates a period of January–March, quarter II: April till June, quarter III: July–September, quarter IV: October – December. a – significant difference between vitamin D concentrations in the IIIrd versus the IVth quarter, p=0.018 (Kruskall-Wallis' test)

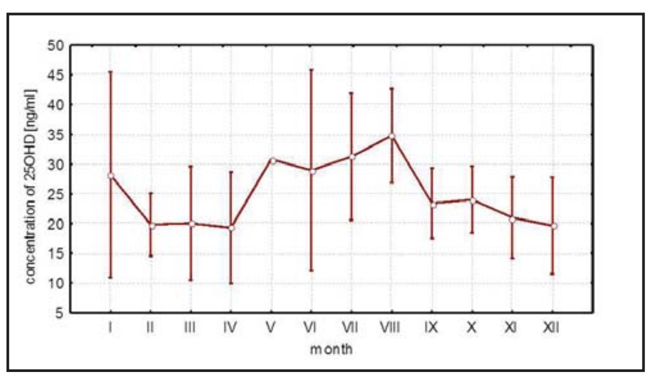

Fig. 3. Concentrations of vitamin D during subsequent months

However, the seasonal variation of vitamin D concentration is not always observed in Polish women. For instance, in a recent study performed in a group of 150 pregnant women from Warsaw, there was no statisti-

Tab. 2. Duration of pregnancy, mode of delivery and status of newborns, stratified according to maternal vitamin D concentrations (mean±SD).

	Group with vitamin D deficiency	Group with vitamin D insufficiency	Group with optimal concentration of vitamin D	*p*-value
% of women	39.4%	29.4%	31.2%	NS
% of women with gestational diabetes	0	3.33%	6.67%	NS
% of women with hypertension	1.67%	5.0%	5.0%	NS
Duration of pregnancy [weeks]	38.8±2.0	39.3±1.2	39.3±1.6	NS
Apgar score	8.9±1.2	9.1±0.6	9.4±0.5	NS
Body mass of newborn [g]	3504±549	3341±431	3320±531	NS
Length of newborn [cm]	55.5±4.0	55.4±2.9	55.4±2.9	NS
% of cesarean section	13.3%	11.7%	20%	NS
% of physiological delivery	20%	15%	20%	NS

NS – not significant

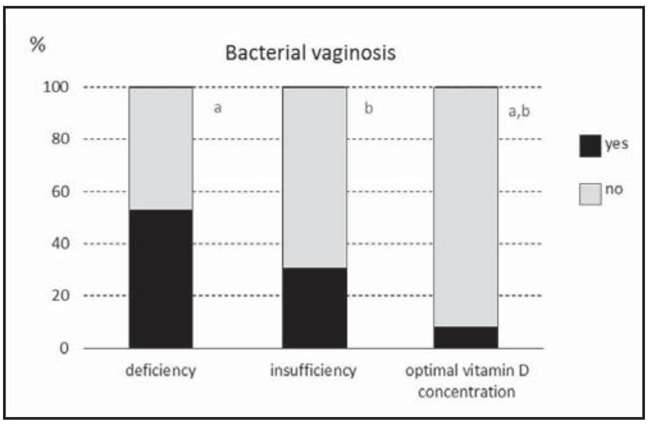

Fig 4. Incidence of bacterial vaginosis depending on vitamin D status.
a – significant difference in bacterial vaginosis incidence between the group of women with vitamin D deficiency and with optimal vitamin D concentrations (p=0.041);
b – significant differences in bacterial vaginosis incidence between women with vitamin D insufficiency and with optimal vitamin D concentrations (p=0.002).
Differences in bacterial vaginosis incidence between women with vitamin D deficiency and insufficiency did not reach the border of statistical significance (p=0.517) – Chi-square test.

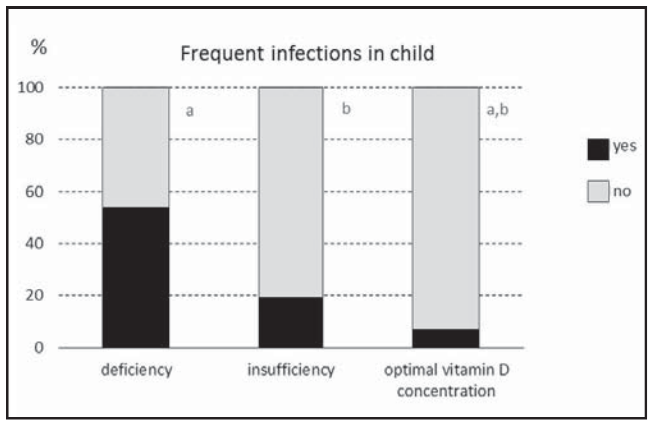

Fig 5. Incidence of recurrent respiratory infections in children, depending on vitamin D status in mother during pregnancy.
a – significant differences in incidence of recurrent infections in children were observed between the group of children born from mothers with vitamin D deficiency and with optimal vitamin D concentrations (p=0.003);
b – significant differences in incidence of recurrent infections between children of mothers with vitamin D insufficiency and with optimal vitamin D concentrations (p=0.040).
There was no difference between children of mothers with vitamin D deficiency and insufficiency (p=0.200) – Chi-square test.

cally significant differences between concentrations of 25(OH)D levels in winter *versus* summer (Bartoszewicz *et al.* 2013). Possible explanation for this discrepancies might be related to differences in oral vitamin D supplementation and voluntary avoidance of sun exposure, declared by women in the study (Bartoszewicz *et al.* 2013). Therefore, we suggest that the presence of a link between season and concentration of 25(OH)D, suggests that in our group the skin synthesis, rather than regularly taken oral supplementation, remains the major source of vitamin D. This is an argument proving inefficiency of vitamin D supplementation in Polish women during pregnancy.

We have also shown significantly higher incidence of bacterial vaginosis in women with vitamin D deficiency. Bacterial vaginosis involves replacement of physiological vaginal microflora by anaerobic bacteria. Such condition may promote development of pregnancy-related complications, including amniotic fluid infections, preterm birth, and infections in newborns (Koumans *et al.* 2007). Previously reported linear inverse dose-dependent relationship between vitamin D levels in pregnant women and bacterial vaginosis was also confirmed (Bodnar *et al.* 2009). The mechanism of action of vitamin D in terms of a contribution towards development of this complication remains unclear. One can speculate, however, that calcitriol influences both the innate and adaptive functions of the immune system (Gunville *et al.* 2013). Vitamin D modulates the expression of peptides, such as cathelicidin, displays an

Copyright © 2014 Neuroendocrinology Letters ISSN 0172–780X • www.nel.edu

activity against viruses and bacteria, and thus helps to reduce the severity of infections and intensity of viral replication (Gunville *et al.* 2013). Moreover vitamin D influences the inflammatory cascade via NFκB and regulates adaptive capacities of immune system, particularly T cells (Gunville *et al.* 2013). In our study bacterial vaginosis seems to be the most important consequence of hypovitaminosis D for health of pregnant women; however we did not observe higher incidence of other disorders previously described in medical literature, including gestational diabetes or preeclampsia (Bodnar *et al.* 2007; Møller *et al.* 2012; Senti *et al.* 2012). This might be a consequence of overall low incidence of these complications in the studied subjects. There were also no significant differences in the mode of delivery, regardless of supply of vitamin D. However, other authors suggest an increased number of cesarean sections in women with vitamin D deficiency, as a consequence of calcium deficiency on muscles (Scholl *et al.* 2012).

We observed a trend towards to higher Apgar scores in children of mothers with normal levels of vitamin but this failed to reach statistical significance. Farther, results of the present study do not permit us to confirm the hypothesis of possible link between the supply of vitamin D in pregnancy on the parameters employed in order to assess size of a newborn. Both body length and birth weight did not differ between the groups of women with normal and reduced levels of vitamin D. In turn, in literature there appeared an observation about differences in sizes of children born in different seasons of the year; and so children born from October to April were larger and heavier than children born from May to September, whereas the authors interpreted this phenomenon as a consequence of variable supply of vitamin D in different seasons (Krenz-Niedbała *et al.* 2011).

In current work the possible effect of vitamin D deficiency on the health of the child was reflected in reduced incidence of respiratory infections in children of mothers with normal supply of vitamin D during pregnancy versus those whose mothers had been vitamin D deficient/insufficient. The above mentioned lower incidence of infections in children, whose mothers had been vitamin D sufficient can be interpreted as a result of immunomodulatory actions of vitamin D (Gunville *et al.* 2013), as in the case of an impact of vitamin D status on development of bacterial vaginosis in pregnant women. The obtained results can also support the hypothesis about possible impact of vitamin D on the phenomenon of fetal programming (Barker *et al.* 2002). According to this hypothesis, environmental factors, including vitamin D may affect the genomic programming during fetal and neonatal period and subsequently modulate the risk of developing certain diseases both in childhood and adulthood (Barker *et al.* 2002). This hypothesis is supported by higher prevalence of asthma and wheezing in children of women with previous vitamin D deficiency in pregnancy (Bodnar *et al.* 2009). Similar data were obtained with regard to an increased risk of developing schizophrenia, multiple sclerosis and type 1 diabetes in children of women with low levels of vitamin D during pregnancy (Hypponen *et al.* 2001; McGrath *et al.* 2004).

In conclusion, our study provides data on the extent of vitamin D deficiency in the population of Polish pregnant women, while providing two categories of data, i.e. objective laboratory results indicating deficiency of vitamin D during pregnancy in a substantial percentage of population of pregnant women, coupled with potential consequences of such deficiency in mothers and their offspring. The latter data, specially affecting recurrent infections in children must be, however, interpreted with caution, given limitations of survey method of data collection; and subjective assessment made retrospectively by women included in the study. However, the studied group was relatively homogenous i.e. only healthy women were included, hence the obtained data may suggest a role of vitamin D in the prevention of infections, both in pregnant women and in their children. It is worth to remind that supplementation of vitamin D in pregnancy is still matter of debate; although modest doses of vitamin D in pregnancy are relatively safe, there are no long-term data about effects on offspring health (Harvey *et al.* 2014). Long-term follow-up of mothers and children who have taken the vitamin D supplementation is needed.

CONCLUSIONS

1. The current model of vitamin D supplementation in pregnant women in Poland is insufficient, particularly in winter months. 2. Vitamin D deficiency in pregnant women fosters development of bacterial vaginosis during pregnancy, and subsequent respiratory infections in children, thus suggestive of a role of vitamin D in prevention of certain infections.

ACKNOWLEDGEMENT

The study was financially supported by the Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland (Project No. 2011/V/2).

REFERENCES

1 Barker DJ, Eriksson JG, Forsen T, Osmond C (2002). Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol **31:** 1235–1239.
2 Bartoszewicz Z, Kondracka A, Krasnodebska-Kiljańska M, Niedźwiedzka B, Popow M, Ambroziak U *et al.* (2013). Vitamin D insufficiency in healthy pregnant women living in Warsaw. Ginekol Pol **84:** 363–367.
3 Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM (2007). Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab **92:** 3517–3522.
4 Bodnar LM, Krohn MA, Simhan HN (2009). Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. J Nutr **139:** 1157–1161.

5 Bojar I, Owoc A, Humeniuk E, Wierzba W, Fronczak A (2012). Inappropriate consumption of vitamins and minerals by pregnant women in Poland. Ann Agric Environ Med **19:** 263–266.
6 Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ *et al.* (2011). Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics **127:** e180–187.
7 Grzechocinska B, Dabrowski FA, Cyganek A, Wielgos M (2013). The role of vitamin D in impaired fertility treatment. Neuroendocrinol Lett **34:** 756–762
8 Gunville GF, Mourani PM, Ginde AA (2013). The role of vitamin D in prevention and treatment of infection. Inflamm Allergy Drug Targets **12:** 239–245.
9 Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R *et al.* (2014). Vitamin D supplementation in pregnancy: a systematic review. Health Technol Assess **18:** 1–190.
10 Holick MF (2009). Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol **19:** 73–78.
11 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP *et al.* (2011). Endocrine Society Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab **96:** 1911–1930.
12 Hypponen E, Laara E, Reunanen A, Jarvelin M, Virtanen SM (2001). Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. **358:** 1500–1503.
13 Koumans EH, Sternberg M, Bruce C, McQuillan G, Kendrick J, Sutton M *et al.* (2007). The prevalence of bacterial vaginosis in the United States, 2001-2004: associations with symptoms, sexual behaviors, and reproductive health. Sex Transm Dis **34:** 864–869.
14 Kovacs CS, Kronenberg HM (1997). Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation. Endocr Rev **18:** 832–872.
15 Krenz-Niedbała M, Puch EA, Kościński K (2011). Season of birth and subsequent body size: the potential role of prenatal vitamin D. Am J Hum Biol **23:** 190–200.
16 McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Jarvelin MR *et al.* (2004). Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res **67:** 237–245.
17 Møller UK, Streym S, Heickendorff L, Mosekilde L, Rejnmark L (2012). Effects of 25OHD concentrations on chances of pregnancy and pregnancy outcomes: a cohort study in healthy Danish women. Eur J Clin Nutr **66:** 862–868.
18 Novakovic B, Galati JC, Chen A, Morley R, Craig JM, Saffery R (2012). Maternal vitamin D predominates over genetic factors in determining neonatal circulating vitamin D concentrations. Am J Clin Nutr **96:** 188–195.
19 Osmola-Mańkowska A, Silny W, Dańczak-Pazdrowska A, Olek-Hrab K, Mańkowski B, Osmola K, Hojan-Jezierska D *et al.* (2012). The sun - our friend or foe? Ann Agric Environ Med **19:** 805–809
20 Pawley N, Bishop NJ (2004). Prenatal and infant predictors of bone health: the influence of vitamin D Am J Clin Nutr. **80** (suppl): 1748S–1751S.
21 Płudowski P, Karczmarewicz E, Bayer M, Carter G, Chlebna-Sokół D, Czech-Kowalska J *et al.* (2013). Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe - recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol **64:** 319–327.
22 Pluta A, Karwicki M, Prószyńska K, Lorenc R, Zalewski T (1987). Systemic sources of vitamin D in mothers and their infants at birth, depending on the season of the year [in Polish]. Pol Tyg Lek **42:** 254–256.
23 Scholl TO, Chen X, Stein P (2012). Maternal vitamin D status and delivery by cesarean. Nutrients **4:** 319–330.
24 Senti J, Thiele DK, Anderson CM (2012). Maternal vitamin D status as a critical determinant in gestational diabetes. J Obstet Gynecol Neonatal Nurs **41:** 328–338.
25 Skowrońska-Jóźwiak E, Adamczewski Z, Tyszkiewicz A, Krawczyk-Rusiecka K, Lewandowski K, Lewiński A (2014). Assessment of adequacy of vitamin D supplementation during pregnancy. Ann Agric Environ Med **21:** 198–200.

Copyright © 2014 Neuroendocrinology Letters ISSN 0172–780X • ***www.nel.edu***