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Placental Calcification and Vitamin D Deficiency in Low-Risk Pregnant Women

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Abstract

Background: The placental calcification is often considered as a physiologic aging process of the placenta but it may be accompanied with the altered levels of vitamin D (vit D). The aim of this study was to evaluate association between placental calcification and vit D in low risk pregnant women.

Materials and Methods: In a case-control study eighty otherwise healthy pregnant women with a gestational age between 37-41 weeks were recruited and divided into the case (n=40), and control (n=40) groups (based on the result of the ultrasonography and according to the Grannum grading). The serum of calcium in pregnant women and vit D level in cord blood were measured by high performance liquid chromatography (HPLC). Neonatal anthropometric values were measured after birth, too.

Results: Most of the pregnant women (n=74, 92%) showed either insufficiency or deficiency of vitamin D in cord while calcium levels were normal in both groups. Serum calcium showed a significant difference between two groups [p=0.042, odds ratio (OR): 2.006, 95% confidence interval (CI): 1.024-3.928], but vitamin D did not (p=0.144, OR: 1.048, 95%CI: 0.984-1.115). Vitamin D level had a significant relationship with calcification of the placenta as well as maternal age, gestational age, and birth weight.

Conclusion: It is better to measure calcium and vitamin D in mothers with calcified placenta because the vitamin D level had a significant relationship with placental calcification and we recommend the administration of vitamin D in pregnant women.

Key Words: Calcification, Calcium, Placenta, Pregnancy, Vitamin D.

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1- INTRODUCTION

Vitamin D is a steroidal hormone and may be found in many organs of the human body. There are two forms of vitamin D in the body: 1) Ergocalcifero (vitamin D2) which is present in plants and some fishes, and 2) Cholecalciferol (vitamin D3) that is produced by 7-dehydrocholesterol and UV in the skin. Vitamin D3 is the main source of vitamin D in humans. It is hydroxylated in the liver [25(OH) D], and then in the kidney to be biologically active [1, 25(OH) D]. The main form of vitamin D in the circulation is 25(OH) D and is considered as the primary index for vitamin D (1). The prospective studies have shown that vitamin D consumption could result in a decrease in chronic diseases like type one diabetes in newborns and children (1, 2). Some recent data show a high prevalence of vitamin D either in adults and children or pregnant women and newborns (3-5). The risk factors of vitamin D deficiency and rickets (as a result of the deficiency) in the first years of life are breastfeeding without vitamin D supplementation, the season of the year, geographical region, and maternal vitamin D deficiency (1).

Many pregnant women show vitamin D deficiency and their newborns have the same condition (5-8). In some studies, race differences show a significant role in the level of circulatory vitamin D. For producing vitamin D, the time for staying in the sunlight for darker skins is four to five times more than others (9). For pregnant women, daily use of at least 1000 IU vitamin D is necessary to reach adequate levels of 25(OH) vitamin D (10). Maternal use of vitamin supplements could not make a significant change in the level of vitamin D of the umbilical cord. So, using multivitamin supplements in pregnancy is not effective for eliminating vitamin D deficiency in pregnant women (11-14). In a systematic review, Harvey et al. reported that there is not enough evidence to establish a clear relationship between vitamin D and the newborns' condition at birth or even recommending vitamin D supplements; so, more research in this field is needed (15).

Calcium metabolism in pregnancy can be summarized as below:

- Total calcium is decreased due to hypoalbuminemia,
- No change in ionized calcium concentration happens,
- 1, 25 (OH) vitamin D is produced in the placenta and more enteric calcium absorption will happen as a result,
- Calcium passes the placenta using the parathyroid hormone, and active transfer mechanism.

The level of 1, 25 (OH) vitamin D and 25 (OH) vitamin D during pregnancy is dramatically increased (16-19), but in pregnant women, producing an active form of 1, 25 (OH) vitamin D could not result in increasing parathyroid hormone as much as non-pregnant women (16, 18-20). Placenta has an important role in metabolism and transfer of vitamin D during the fetal period. Metabolism of vitamin D is a complex relationship between the mother, the placenta and the fetus. Placental calcification is a condition in which accumulation of calcium is found in the placental tissue mostly through Ultrasonography (21-22). The possibility of placental calcification is increased when pregnancy gets older and is usually seen after the 36th week. The calcification before the 36th week is usually known as preterm placental calcification; so, the placenta may play a role as the main regulator of vitamin D production during pregnancy (23). The placental calcification is often considered as a physiologic aging process of the placenta (23, 24), but could be a type of pathologic change due to environmental factors. Predisposing factors for the placental calcification include smoking (23, 25-29), younger age

of mother (6, 8, 9), and the lower count of pregnancies (25, 26, 30) even though there are discrepancies about the smoking effect (31). A calcified placenta may be accompanied by the lower levels of vitamin D, so, calcification of the placenta and the vitamin D levels of the umbilical cord may show a relationship (32). The high prevalence rate of vitamin D deficiency in pregnant women is worrying (33). The estimated rate is about 84.4% in Iran (34), 99% in Turkey (35, 36), and 85% in India (37). In a few investigations in the US, vitamin D levels in pregnant women were shown as enough and those women had consumed dairy products four times more than others (38, 39).

Measurement of the vitamin D levels is not recommended as a part of comprehensive screening in pregnancy yet. Methods of measurement are different and the normal level is not consistent in all measurements. Some believe that vitamin D level of more than 20 ng/dL is enough for the newborn (40); while new reports consider the level as 40 ng/dL (41). Placenta has an important role in vitamin D metabolism in the fetal period and some independent factors increase the risk of placental dysfunction and effect on fetal vitamin D metabolism (42-44). Placental calcification (also known as placental aging) is a type of common pathologic change and happens in about half of the pregnancies (45).

Calcium deposits in the placenta may result in pregnancy complications i.e. fetal distress, limited intrauterine growth, and anomalies. Cause of the calcification is not clearly recognized but it might be a combination of genetic and environmental factors like radiation and drug adverse effect (46). In this study, we investigated any association between the placental calcification and the level of vitamin D in the umbilical cord in full-term pregnancies without risk factors. Also, we studied the relationship between vitamin D levels and maternal factors (e.g. serum calcium level) as well as neonatal anthropometric factors (e.g. weight, height, head circumference, and Apgar score).

2- MATERIALS AND METHODS

2-1. Research setting and population

In a case-control study, 80 otherwise healthy pregnant women with a gestational age between 37 and 41 weeks (13) were recruited from November 2017 to March 2018 in Qazvin, Iran. All women were residents of the city of Qazvin and referred to the Kosar Hospital, a women-specific referral, and tertiary level teaching hospital. Sample was enrolled with the non-random sampling method. The participants became aware of the objectives of the research and completed the informed consent form. Exclusion criteria were smoking, drinking alcohol, taking Vitamin D during pregnancy, systemic hypertension, diabetes mellitus, post-term pregnancy, chronic hepatic or renal disease, severe anemia (Hb < 7 mg/dL), thyroid or parathyroid dysfunction, and Placenta previa.

2-2. Clinical and laboratory measurements

All participants were assessed with ultrasonography at the time of enrollment in the study. Based on the result of the ultrasonography and according to the Grannum grading, we divided them into two groups: a) case group (n = 40) who showed a grade II or III calcified placenta, and b) control group (n = 40) who did not show calcified placenta. The two groups were matched based on the type of delivery because of the importance of the factor [both groups consisted of 26 (65%) normal vaginal delivery (NVD), and 14 (35%) cesarean section (C/S)]. Other possible confounders were not matched and were left for adjustment through the statistical analysis (logistic regression). Maternal blood samples were collected from the antecubital vein in the morning

and after 10 hours of fasting and the cord blood sample was collected immediately after delivery. In the both samples, the blood volume was 3 ml. Serum samples were centrifuged first (5000 rounds per minute for 15 – 20 minutes), then frozen quickly and stored at -80 ℃ until the final analysis. Since 25(OH) D is the best indicator of stored Vitamin D level (15, 47), we measured 25(OH) D in the participants. The Vitamin D level of the cord blood was measured by HPLC in a private lab with a normal level of 30 ng/mL. Serum calcium was also measured with a normal range of 8.6 to 10.3 mg/dL. Anthropometric values of the newborns were measured after birth. Neonatal weight was measured by a neonatal/pediatric scale, as well as height from vertex to heel and head circumference from occipital to frontal by a measuring tape. Apgar score was recorded in the first and fifth minutes.

2-3. Ethical considerations

All information about the objectives and methods of the study were shared with the participants and their questions were answered. Informed consent was obtained from all participants. Personal information i.e. identification and clinical data remained secured for research purposes only. All aspects of the study were in accordance with national research ethical codes and WMA Helsinki declaration. This study was approved in Qazvin University of Medical Sciences Ethics Committee with the ID IR.QUMS.REC.1396.34.

2-4. Data analyzed

After collecting data, SPSS software version 23.0 was used for descriptive analyses and logistic regression to find out effective variable on placental calcification. Level of significance was considered as 0.05.

3- RESULTS

With a case-control design, we enrolled 40 pregnant women with the calcified placenta (case group), and 40 with the non-calcified placenta (control group). **Table.1** shows the baseline characteristics of the participants.

Table-1: Baseline characteristics of the participants in the study groups.

Variables		Case group (n = 40)		Control group (n = 40)		Overall (n = 80)		p-value
		Mean	SD	Mean	SD	Mean	SD	
Maternal age		23.98	5.96	26.35	5.07	25.16	5.63	0.059
Gestational Age		39.59	1.67	38.88	2.27	39.23	2.01	0.115
Birth weight		3293.88	357.87	3457.38	345.49	3375.63	359.05	0.041
Birth height		49.79	2.20	50.60	2.00	50.20	2.13	0.093
Birth head circumference		34.13	1.43	34.76	1.39	34.45	1.43	0.05
Calcium		8.97	0.77	8.63	0.61	8.80	0.71	0.030
Vitamin D		15.91	11.03	12.64	5.41	14.28	8.79	0.754
APGAR score (median)		9		9		9		1.0
		Number	%	Number	%	Number	%	P-value
Gender	Male	17	42.5	21	52.5	38	47.5	0.502
	Female	23	57.5	19	47.5	42	52.5	

SD: Standard deviation.

Based on the normal range and participants' levels of vitamin D and calcium, most of the pregnant women showed either insufficiency or deficiency of vitamin D while calcium levels were normal in most of the participants of both groups. **Table.2** shows the distribution of vitamin D and calcium levels in each group and total.

Table-2: The distribution of vitamin D level (ng/mL) and calcium in each group and total.

Variables	Level	Case (n = 40)		Control (n = 40)		Overall (n = 80)		P-value
		Number	%	Number	%	Number	%	
Vitamin D*	< 20	35	87.5	28	70	63	78.8	0.032
	20-30	5	12.5	6	15	11	13.8	
	>30	0	0	6	15	6	7.5	
	Total	40	100	40	100	80	100	
Calcium**	<8.5	11	28.2	19	47.5	30	38	0.105
	≥ 8.5	28	71.8	21	52.5	49	62	
	Total	39	100	40	100	79	100	

*: Vitamin D levels: deficiency: less than 20 ng/mL, insufficiency: 21-29 ng/mL, sufficiency: 30 ng/mL and above (48). **: Calcium levels: hypocalcemia: <8.5 mg/dL, normal: 8.5 to 10.2 mg/dL, hypercalcemia: >10.2 (48).

For determining the difference between two groups of the study, we used binary logistic regression method. With placental calcification as the dependent factor and a backward stepwise method (Wald), we initially entered calcium and vitamin D levels in the model. Serum calcium showed a significant difference between two groups [p = 0.042, odds ratio (OR) = 2.006, confidence interval (CI) 95%: 1.024 – 3.928] but vitamin D did not (p = 0.144, OR = 1.048, CI 95%: 0. 984 - 1.115). After entering all variables in the model (i.e. vitamin D and calcium levels, maternal age, gravidity, gestational age (GA), birth weight, height, and head circumference, gender, Apgar score, and nationality), vitamin D level showed a significant relationship with calcification of the placenta as well as maternal age, gestational age, and birth weight. Other variables did not show any relationship with placental calcification. Final variables with a significant relationship with placental calcification are listed in **Table-3**.

Table-3: Relationship between levels of vit D, maternal age, gestational age and birth weight with placental calcification.

Variables	P-value	Odds ratio (OR)	Confidence interval (CI 95%) for OR
Vitamin D level	0.022	1.097	1.013 - 1.187
Maternal age	0.025	0.889	0.802 - 0.985
Gestational age	0.048	1.544	1.004 - 2.373
Birth weight	0.009	0.998	0.996 - 0.999

4- DISCUSSION

Vitamin D deficiency is a preventable public health problem. Adequate levels of vitamin D are essential for fetal and maternal health. Placental calcification in full-term pregnancy is an ultrasonographic finding and is considered as physiologic. The current study was based on the idea of the relationship between placental calcification and maternal factors i.e. the level of blood calcium and vitamin D. Such a relationship may provide

information about determinants of placental calcification and its potential risk factors in pregnant women. Our study showed a low level of vitamin D in cord blood of pregnant women; most of them were deficient (78.8%, n=63), and only 7.5% (n=6) had a sufficient level. At the same time, the mean concentration of vitamin D was lower in the control group (12.64 vs. 15.91 ng/ml), and 15% (n=6) of the control women had a sufficient level (compared to zero in case group). This is especially important because both placental calcification and vitamin D deficiency may have a relationship with complications such as preeclampsia (49), gestational diabetes (50), and intrauterine growth retardation (IUGR) (22).

Vitamin D deficiency may increase the risk of low birth weight, neonatal rickets, and hypocalcemia as well as asthma and diabetes mellitus. It may also have adverse effects on neuronal growth and the child's immune system in the future. Therefore, it is important to avoid the deficiency of vitamin D in pregnant women. Benedir et al. in their study showed that the mean level of vitamin D in the case group was lower, but the difference was not significant (48). In the current study, we did not find a relationship between vitamin D status and somatic growth of the newborn. Rodriguez et al. and Eggemoen et al. did not find any relationship between anthropometric parameters and vitamin D levels even though vitamin D deficiency was found in 51% of the women (51, 52). Also, Shakiba et al., and Josefson et al. did not find any relationship between cord vitamin D levels and neonatal weight and height (53, 54) which was compatible with our results. In contrast, Lykkedegn et al. showed a U-shaped relationship between neonatal weight and vitamin D concentration of the cord (55). Also, they reported a significant weight gain when vitamin D concentration was above 24 ng/ml which is different from what we found. A meta-analysis of observational studies showed that low concentration of vitamin D (< 15ng/ml) may result in lower birth weight (about 131 g) with no effect on the height and head circumference (56).

4-1. Limitations of the study

Inadequate sample size could be a potential limitation of the study that resulted in non-significant differences between the groups. Another potential limitation is that vitamin D analysis was done as a single test and immediately after birth in this study. For this reason, it is not easy to be sure that the measured vitamin D concentration was a good representative of the whole embryonic process. The final issue of the study is limited information about the rate of exposure in the sunshine and skin color of the individuals which could affect vitamin D levels.

5- CONCLUSION

Placental calcification is a pathological process that can provide information on vitamin D and calcium in pregnancy. Vitamin D has different effects and functions in the body and rather than the anthropometric measurements, long-term growth and health status assessment of the children could be a reasonable suggestion for the subsequent studies. According to association between placental calcification and vitamin D levels in the neonate, it is better to prescribe vitamin D to mothers in case of abnormal placental calcification during pregnancy.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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8- REFERENCES

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Endocrine Society. Evaluation, Treatment, and Prevention of vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011; 96(7):1911.

2. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol. 2010; 10:482–96.

3. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared to 2000–2004. Am J Clin Nutr. 2008; 88:1519–1527.

4. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. Pediatrics. 2009; 124:362–370.

5. Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin D deficiency in a healthy group of mothers and newborn infants. Clin Pediatr (Phila) 2007; 46:42–4.

6. IOM (Institute of Medicine) Dietary Reference Intakes for Calcium and vitamin D. Washington, DC: The National Academies Press; 2011.

7. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr.2008;88(2):582S–586S.

8. Hollis BW, Wagner CL. vitamin D deficiency during pregnancy: an ongoing epidemic. Am J Clin Nutr. 2006; 84:273.

9. Clemens TL, Henderson SL, Adams JS, Holick MF. Increased skin pigment reduces the capacity of the skin to synthesize vitamin D3. Lancet. 1982;319(8263):74–76.

10. Wagner CL, Greer FR. and the Section on Breastfeeding and Committee on Nutrition. Prevention of Rickets and vitamin D Deficiency in Infants, Children, and Adolescents. Pediatrics. 2008; 122:1142–52.

11. Datta S, Alfaham M, Davies DP, Dunstan F, Woodhead S, Evans J, et al. vitamin D deficiency in pregnant women from a non-European ethnic minority population–an interventional study. BJOG.2002;109(8):905–8.

12. Madelenat P, Bastian H, Menn S. Winter supplementation in the 3rd trimester of pregnancy by a dose of 80,000 IU of vitamin D. J Gynecol Obstet Biol Reprod. 2001;30(8):761–67.

13. Kalra P, Das V, Agarwal A, Kumar M, Ramesh V, Bhatia E, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. Br J Nutr. 2012;108(6):1052–58.

14. De-Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. The Cochrane Collaboration: Published by John Wiley & Sons, Ltd; 2012. pp. 1–61.

15. Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R, et al. vitamin D supplementation in pregnancy: a systematic review. Health Technol Assess.2014; 45:1–190.

16. Gertner JM, Coustan DR, Kliger AS, Mallette LE, Ravin N, Broadus AE.. Pregnancy as a state of physiologic absorptive hypercalciuria. Am J Med 1986; 81:451.

17. Seki K, Makimura N, Mitsui C, et al. Calcium-regulating hormones and osteocalcin levels during pregnancy: a longitudinal study. Am J Obstet Gynecol 1991; 164:1248.

18. Seely EW, Brown EM, DeMaggio DM, Weldon DK, Graves SW. A prospective study of calciotropic hormones in pregnancy and post-partum: reciprocal changes in serum intact parathyroid hormone and 1,25-dihydroxy vitamin D. Am J Obstet Gynecol 1997; 176: 214.

19. Bikle DD, Gee E, Halloran B, Haddad JG. Free 1,25-dihydroxy vitamin D levels in serum from normal subjects, pregnant

subjects, and subjects with liver disease. J Clin Invest 1984; 74:1966.

20. Ardawi MS, Nasrat HA, BA'Aqueel HS. Calcium-regulating hormones and parathyroid hormone-related peptide in normal human pregnancy and postpartum: a longitudinal study. Eur J Endocrinol 1997; 137:402.

21. Torel Ergur A, Berberoglu M, Atasay B, et al. vitamin D deficiency in Turkish mothers and their neonates and in women of reproductive age. J Clin Res Pediatr Endocrinol 2009;1(6): 266–9.

22. Grannum PA, Berkowitz RL, Hobbins JC. The ultrasonic changes in the maturing placenta and their relation to fetal pulmonic maturity. Am J Obstetr Gynecol 1979;133:915–22.

23. Harris RD, Alexander RD. Ultrasound of the placenta and umbilical cord. In Ultrasonography in Obstetrics and Gynecology, Callen PW (ed.). W.B. Saunders: Philadelphia, PA, 2000; 602–4.

24. Nolan RL. The placenta, membranes, umbilical cord, and amniotic fluid. In A Practical Guide to Ultrasound in Obstetrics and Gynecology, Sauerbrei EE, Nguyen KT, Nolan RL (eds). Lippincott-Raven: Philadelphia, PA, 1998; 438–39.

25. McKenna D, Tharmaratnam S, Mahsud S, Dornan J. Ultrasonic evidence of placental calcification at 36 weeks' gestation: maternal and fetal outcomes. Acta Obstet Gynecol Scand 2005; 84: 7–10.

26. Proud J, Grant AM. Third-trimester placental grading by ultrasonography as a test of fetal wellbeing. BMJ 1987; 294: 1641–44.

27. Klesges LM, Murray DM, Brown JE, Cliver SP, Goldenberg RL. Relations of cigarette smoking and dietary antioxidants with placental calcification. Am J Epidemiol 1998; 147: 127–35.

28. Brown HL, Miller JM Jr, Khawli O, Gabert HA. Premature placental calcification in maternal cigarette smokers. Obstet Gynecol 1988; 71: 914–17.

29. Christianson RE. Gross differences observed in the placentas of smokers and non-smokers. Am J Epidemiol 1979; 110: 178–18.

30. Spirt BA, Cohen WN, Weinstein HM. The incidence of placental calcification in normal pregnancies. Radiology 1982;142: 707–11.

31. Vosmar MB, Jongsma HW, van Dongen PW. The value of ultrasonic placental grading: no correlation with intrauterine growth retardation or with maternal smoking. J Perinat Med 1989; 17: 137–43.

32. Bedir Findik R, Ersoy AO, Fidanci V, Tasci Y, Helvacioglu Y, Karakaya J. vitamin D deficiency and placental calcification in low-risk obstetric population: are they related? J Matern Fetal Neonatal Med. 2016 Oct;29(19):3189-92.

33. Poel YHM, Hummel P, Lips P, Stam F, Ploeg TV, Simsek S. Vitamin D, and gestational diabetes: A systematic review and meta-analysis. European J of Int Med. 2012 Jul; 23(5): 465-9.

34. Tabrizi R, Moosazadeh M, Akbari M, Dabbaghmanesh MH, Mohamadkhani M, Asemi Z, et al. High Prevalence of vitamin D Deficiency among Iranian Population: A Systematic Review and Meta-Analysis. Iran J Med Sci. 2018; 43(2): 125–39.

35. Halicioglu O, Aksit S, Koc F, Sezin A, Akman SA, Albudak E, et al. vitamin D deficiency in pregnant woman and their neonates in springtime in western Turkey. Paediatr Perinat Epidemiol. 2012; 26:53–60.

36. Kılıcaslan AÖ, Kutlu R, Kilinc I, Ozberk DI. The effects of vitamin D supplementation during pregnancy and maternal vitamin D levels on neonatal vitamin D levels and birth parameters. J Matern Fetal Neonatal Med.2017; 25:1–8.

37. Sathish P, Raveendran S, Padma R, Balakrishnan D, Muthusami M. Correlation between maternal and neonatal blood vitamin D levels and its effect on the newborn anthropometry. Int J Reprod Contracept Obstet Gynecol.2016; 5:2983–88.

38. Zhang C, Qiu C, Hu FB, David RM, van Dam RM, Bralley A, et al. Maternal Plasma 25-Hydroxyvitamin D Concentrations and the Risk for Gestational Diabetes Mellitus; PLoS ONE 2008; 3(11) 37-53.

39. Baker AM, Haeri S, Camargo Jr CA, Stuebe, Bogess KA. First-trimester Maternal vitamin D status and risk for gestational diabetes mellitus: a nested case-control study. Diabetes Metab Res Rev. 2012;28(2):164-8.

40. Streym VS, Moller KU, Rejnmark L, Heickendorff L, Mosekilde L, Vestergaard P. Maternal and infant vitamin D status during the first 9 months of infant life – a cohort study. Eur J Clin Nutr.2013; 67:1022–28.

41. Hollis BW, Wagner CL. New insights into the vitamin D requirements during pregnancy. Bone Res.2017; 5:17030.

42. Hochberg Z, Bereket A, Davenport M, et al. Consensus development or the supplementation of vitamin D in childhood and adolescence. Horm Res 2002;58: 39–51.

43. Reese LE, Chesney RW, De Luca HF. vitamin D of human milk identification of biologically active forms. Am J Clin Nutr 1982;36:122–6.

44. Cho GJ, Hong SC, Oh MJ, Kim HJ. vitamin D deficiency in gestational diabetes mellitus and the role of the placenta. Am J Obstet Gynecol 2013;209: 560.e1–8.

45. Spirt BA, Cohen WN, Weinstein HM. The incidence of placental calcification in normal pregnancies. Radiology. 1982; 142:707–11.

46. Burdan F, Szumilo J, Korobowicz-Markiewicz A, Dyndor K, Szumilo M, Klepacz R. Unusual interleukin-1 and-6 expression in fetal cartilage is associated with placental abnormalities. Folia Histochem Cytobiol. 2010; 48: 30–36.

47. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. IOF Committee of Scientific Advisors (CSA): Nutrition Working Group: Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009; 20(11): 1807–20.

48. Bedir Findik R, Ersoy AO, Fidanci V, Tasci Y, Helvacioglu Y, Karakaya J. Vitamin D deficiency and placental calcification in low-risk obstetric population: are they related? J Matern Fetal Neonatal Med. 2016; 29(19):3189-92.

49. Liu NQ, Ouyang Y, Bulut Y, et al. Dietary vitamin D restriction in pregnant female mice is associated with maternal hypertension and altered placental and fetal development. Endocrinology. 2013; 154(7): 2270-80.

50. Vosmar MB, Jongsma HW, van Dongen PW. The value of ultrasonic placental grading: no correlation with intrauterine growth retardation or with maternal smoking. J Perinatal Med. 1989; 17: 137–43.

51. Rodriguez A, García-Esteban R, Basterretxea M, Lertxundi A, Rodríguez-Bernal C, Iñiguez C, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG. 2015; 122:1695–704.

52. Eggemoen ÅR, Jenum AK, Mdala I, Knutsen KV, Lagerløv P, Sletner L. vitamin D levels during pregnancy and associations with birth weight and body composition of the newborn: a longitudinal multiethnic population-based study. Br J Nutr. 2017; 117: 985–93.

53. Shakiba M, Iranmanesh MR. vitamin D requirement in pregnancy to prevent deficiency in neonates: a randomized trial. Singapore Med J. 2013; 54:285–8.

54. Josefson JL, Reisetter A, Scholtens DM, Price HE, Metzger BE, Langman CB, et al. Maternal BMI associations with maternal and cord blood vitamin D levels in a North American subset of hyperglycemia and adverse pregnancy outcome (HAPO) study participants. PLoS One. 2016; 11(3): e0150221.

55. Lykkedegn S, Beck-Nielsen SS, Sorensen GL, Andersen LB, Fruekilde PBN, Nielsen J, et al. vitamin D supplementation, cord 25-hydroxyvitamin D and birth weight: findings from the Odense Child Cohort. Clin Nutr (2017) 36:1621–27.

56. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013; 346: f1169.