Gestational Diabetes Mellitus, Fetal Growth and Vitamin D

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Vitamin D is an important secosteroid hormone in skeletal and non-skeletal systems. Vitamin D has relevance to muscle and immune function, hypertension, diabetes mellitus, cancer, and pregnancy because vitamin D receptors (VDR) are present in many non-skeletal tissues. Vitamin D acts on target tissues via the binding of its active form to VDR. As vitamin D affects not only bone metabolism but also glucose metabolism, vitamin D deficiency may affect the development of gestational diabetes mellitus and fetal growth. Although vitamin D deficiency is prevalent during pregnancy, there are conflicting reports on the effect of vitamin D deficiency on pregnancy complications, such as fetal growth restriction and gestational diabetes. This article reviews published papers on the effects of vitamin D on gestational diabetes and fetal growth.

Key Words: Diabetes, Gestational, Fetal development, Vitamin D

INTRODUCTION

In non-pregnant state, once vitamin D is synthesized from the skin or diet, it binds to vitamin D binding protein (DBP) and is transferred to the liver. Conversion of vitamin D to 25-hydroxy-vitamin D (25[OH]D) through 25-hydroxylation is taken place in the liver. Since the half-life of 25(OH)D is 2 to 3 weeks, serum 25(OH)D reflects the vitamin status of the body. And 25(OH)D is bounded to DBP and enters the circulation to the kidney where take place 1-hydroxylation of 25(OH)D to 1,25 dihydroxy-vitamin D (1,25[OH]2D) by the action of 1α-hydroxylase, and the half-life of 1,25(OH)2D is 8 hr.

In pregnant state, 25(OH)D crosses the placenta and 1,25(OH)2D passes only at low concentrations during pregnancy. However, 1,25(OH)2D of production is increased primarily through the elevation of 1-hydroxylase activity in the placenta and decidua, which is supplied to mother and fetus.[1] Although adequate vitamin D status is important during pregnancy, it is still controversial which level of serum 25(OH)D during pregnancy is optimal. Because the optimal level of serum 25(OH)D during pregnancy was based on the general population,[2,3] the definition of vitamin D deficiency in pregnancy is also to be elucidated. Inadequate maternal vitamin D status has known to be associated with several adverse maternal-fetal outcomes, including pre-eclampsia, gestational diabetes mellitus (GDM), in-

creased rate of primary cesarean section, preterm labor, fetal growth retardation, and neonatal hypocalcemia.[4] However, the effects of vitamin D on maternal-fetal outcomes are different based on several clinical trials. The association between vitamin D and GDM has been investigated in several studies which results were still inconclusive due to factors, such as selection bias, timing and methodology of vitamin D measurement, time of GDM diagnosis and diagnostic criteria for GDM.[5] Since maternal 25(OH)D crosses the placenta during pregnancy, it is assumed maternal vitamin D status could affect fetal bone growth, however, the effect of vitamin D on fetal bone growth during pregnancy is sparsely investigated.

VITAMIN D AND GDM

GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not overt diabetes mellitus (DM) prior to pregnancy. If women are diagnosed with DM in the first trimester, their DM should be stratified as having preexisting type 1 or type 2 diabetes rather than GDM.

As the prevalence of GDM which ranges from 2% to 20% depending on the populations is increasing worldwide [5] and risk for developing DM in the postpartum 10 to 20 years is substantial (35-60%), the interest in GDM is growing rapidly. There are several evidences supporting a role for vitamin D in developing glucose intolerance and type 2 DM. Potential mechanisms of effects of vitamin D on glucose metabolism are as follows; the binding of active form of vitamin D to vitamin D receptors (VDR) on pancreatic beta-cells, the expression of 1-α-hydroxylase in pancreatic

β-cells, insulin secretion and sensitivity by regulating extracellular calcium and calcium flux through the pancreatic β-cell, the presence of vitamin response element in the human insulin gene promoter, the effects on stimulating the expression of insulin receptor and the effects on systemic inflammation by modulating the effects of cytokines for beta cell function,[6] since insulin resistance (IR) and β-cell apoptosis could be induced by systemic inflammation.

The relevant explanation for molecular mechanisms of vitamin D on type 2 DM [7,8] and high prevalence of vitamin D deficiency during early pregnancy [9] applying the definition of vitamin D deficiency (serum 25[OH]D level <20 ng/mL) set forth by Institute of Medicine (IOM) suggest that vitamin D deficiency may associate with the development of glucose intolerance or GDM. Therefore, many studies have been focused on maternal vitamin D level and GDM because GDM is associated with adverse pregnancy outcome such as macrosomia, preeclampsia and cesarean section.[7,10] GDM is diagnosed at the second or third trimester of pregnancy and is therefore likely to be associated with the 25(OH)D status of early pregnancy. Several studies observed the associations between maternal serum 25(OH)D in the first trimester and developing GDM after second trimester were as shown in the Table 1. Boyle et al.[11] showed maternal 25(OH)D levels <30 ng/mL at 15 weeks of gestation were associated with the development of GDM, but after adjustment with body mass index (BMI) and ethnicity, the association was not significant. Park et al.[12] measured maternal 25(OH)D, plasma insulin and glucose at 12 to 14 weeks of gestation followed by calculating homeostatic model assessment (HOMA)-IR

Table 1. Summary of studies on vitamin D status of early pregnancy and GDM

Study design	No. of subjects (nation)	Sampling time for serum 25(OH)D (week)	Time for screening GDM (week)	Outcome (aternal 25[OH]D deficiency vs. GDM)	Reference
Observational study	1,710 (New Zealand)	15	24-28	Not significant association	Boyle, et al. 2016 [11]
Prospective	655 (Canada)	6-13	24-28	Low 25(OH)D associated insulin resistance	Lacroix, et al. 2014 [17]
Prospective	523 (Korea)	12-14	24-28	No association	Park, et al. 2014 [12]
Prospective	674 (USA)	<16	24-28	No association (except smokers)	Tomedi, et al. 2013 [13]
Nested case-control	180 (USA)	11-14	24-28	No association	Baker, et al. 2012 [14]
Case control	1,200 (UK)	11-13	24-28	No association	Savvidou, et al. 2011 [15]
Case control	248 (UK)	First trimester	28±4.6	No association	Makgoba, et al. 2011 [16]
Nested case-control	171 (USA)	16	24-28	Association	Zhang, et al. 2008 [18]

GDM, gestational diabetes mellitus; 25(OH)D, 25-hydroxy-vitamin D; USA, United States of America; UK, United Kingdom.

and HOMA-B which represented IR and β-cell function among 523 Korean pregnant women including GDM and non-GDM. They showed maternal 25(OH)D were not associated with the risk of GDM, IR and β-cell impairment. Tomedi et al.[13] found an association between maternal 25(OH)D and hyperglycemia only among smokers. Several studies reported maternal vitamin D deficiency was not associated with development of GDM.[14-16] In contrast, other studies reported the first trimester maternal vitamin D deficiency was associated with risk for GDM development.[17,18] Although the inverse association between vitamin D status and GDM was accepted in previous studies of meta-analysis,[19,20] those results are still conflicting because of confounding factors such as ethnicity, definition of vitamin D deficiency, sampling time for serum 25(OH)D (1st, 2nd or 3rd trimester) and study types. A recent report on summary of several meta-analyses have not shown a clear answer to the relationship between vitamin D and GDM.[21]

Because the results of association between maternal vitamin D status during early pregnancy and GDM are still inconsistent, more data are needed to clarify the relationship between maternal vitamin D status and GDM.

VITAMIN D AND FETAL GROWTH

Vitamin D is known to be essential for the health of pregnant women and their fetuses. Low maternal 25(OH)D status decreased transfer of 25(OH)D to the fetus, and may result in impaired growth, delayed bone ossification and congenital rickets.[2] Vitamin D deficiency (serum 25[OH]D <20 ng/mL) among pregnant women is common worldwide, however, optimal level of serum 25(OH)D for fetal growth during pregnancy is still unknown. Although suboptimal maternal vitamin D has been known to be associated with adverse pregnancy outcomes including fetal growth restriction, reports regarding the association between maternal vitamin D and fetal bone growth are inconclusive. In several studies, maternal 25(OH)D has been associated with fetal growth, but other studies reported different results (Table 2). Miliku et al.[22] reported that a low 25(OH)D level in mid-trimester pregnancy is associated with a smaller head circumference and shorter body length during third trimester pregnancy, which reflect a fetal growth restriction. Lee et al.[23] found only a correlation between the difference of serum 25(OH)D level between 12 to 14

Table 2. Brief summary of associations of maternal 25(OH)D with fetal growth based on published data

Study design	No. of subjects (nation)	Sampling time for serum 25(OH)D (week)	Parameters	Outcome (maternal 25[OH]D vs. fetal growth)	Reference
Population based prospective study	7,098 (Netherlands)	20.3 (18.5-23.3)	Fetal head circumference, body length	Association	Miliku, et al. 2016 [22]
Prospective longitudinal study	523 (Korea)	12-14 20-22 32-34	Fetal biparietal & occipitofrontal diameter, head & abdominal circumference, femur & humerus length	No association (except growth velocity of fetal biparietal diameter between 20 to 22 and 32 to 34 weeks)	Lee, et al. 2015 [23]
Prospective cohort study	2,382 (Spain)	13.5±2.2	Fetal growth restriction, birth height, head circumference	No association	Rodriguez, et al. 2015 [24]
Prospective cohort study	60 (Ireland)	1) Early pregnancy 2) 28 3) Delivery (cord blood)	Fetal growth	Winter cohort (correlation between early pregnancy 25[OH]D & femur length at 20 weeks, and between 28-week 25[OH]D & femur length at 34 weeks) Summer cohort (no correlation)	Walsh, et al. 2013 [25]
Prospective longitudinal study	171 (≤18 years old) (USA)	1) ~26 2) Delivery	Feta femur & humerus Z-score	Association (when maternal calcium intake <1,050 mg/dL)	Young, et al. 2012 [26]
Longitudinal observational study	357 (UK)	34	FV, PMD	Univariate analysis (25[OH]D ∝ FV, PMD) Multivariate regression analysis (25[OH]D ∝ PMD)	Ioannou, et al. 2012 [27]
Prospective longitudinal study	424 (UK)	34	Fetal femur length, distal metaphyseal cross-sectional area, femoral splaying index	Lower 25[OH]D; 1) not related to fetal femur length, 2) associated with greater femoral metaphyseal cross-sectional area & higher femoral splaying index at 19 weeks' gestation)	Mahon, et al. 2010 [28]

25(OH)D, 25-hydroxy-vitamin D; USA, United States of America; UK, United Kingdom; FV, fetal femur volume; PMD, proximal metaphyseal diameter.

and 20 to 22 weeks and the growth velocity of the fetal biparietal diameter between 20 to 22 and 32 to 34 weeks of gestation. Other parameters for fetal growth were not associated with maternal serum 25(OH)D which were measured at first, second and third trimester. Fetal growth such as fetal biparietal and occipitofrontal diameter, head and abdominal circumference, femur and humerus length using ultrasonography were measured three times during pregnancy to generate growth velocity.[23] Rodriguez et al.[24] compared maternal 25(OH)D levels with fetal growth, birth weight, length, and head circumference, and found that high serum maternal 25(OH)D levels were not statistically significant but tended to have a low head circumference, and not significantly associated between 25(OH)D levels and other birth outcomes. Walsh et al.[25] found a correlation between maternal 25(OH)D in early pregnancy and femur length at 20 weeks of pregnancy, and between maternal 25(OH)D level at 28 weeks and femur length at 34 weeks of pregnancy in winter cohort not in summer cohort. And a shorter infant length was found in those with lower serum 25(OH)D levels (less than the median values) at early pregnancy. Young et al.[26] showed fetal femur and humerus z-score in pregnant women under 18 years old were significantly associated with maternal 25(OH)D in case of maternal calcium intake is less than 1,050 mg/day. Ioannou et al.[27] investigated the relationship between fetal femur volume and maternal vitamin D level, fetal femur volume was measured using femur length, proximal metaphyseal diameter, and midshaft diameter. At 34 weeks of gestation, maternal serum 25(OH)D correlated significantly with fetal femur volume and proximal metaphyseal diameter, however, in multiple regression analysis, maternal serum 25(OH)D was statistically significant only with the proximal metaphyseal diameter. In Mahon et al.'s study[28], maternal 25(OH)D measured at 34 weeks of gestation was compared with fetal femur length and distal metaphyseal cross-sectional area using a high-resolution 3D ultrasound and femoral splaying index reflecting fetal femoral morphology. There was no correlation between low maternal 25(OH)D levels and fetal femur length, but it was associated with higher femoral splaying index (which is commonly observed in childhood rickets) at 19 weeks of gestation. It suggested that vitamin D could affect fetal femoral morphology development from the 19th week of gestation.[28] In a meta-analysis studies, Galthen-Sorensen et al.[29] suggested that low

maternal 25(OH)D may influence fetal bone growth when maternal calcium intake is low and Pérez-López et al.[30] reported that vitamin D supplementation during pregnancy may increase maternal 25(OH)D levels, birth weight, length, but it was not associated with other maternal and fetal outcomes. As aforementioned, it is very hard to answer whether maternal 25(OH)D and fetal bone growth are associated or not, because several factors such as differences in study design, ethnicity, country, 25(OH)D collection time, and the purpose of outcomes may contribute to generate different outcomes.

SUMMARY

Vitamin D has been known as an important hormone in the skeletal & non-skeletal system during pregnancy, but its precise role in pregnancy is still unclear. Although the researches for association between vitamin D and pregnancy outcomes are not still enough to reach consistent results, vitamin D should not be interpreted to have an insignificant effect on pregnancy until large randomized, controlled, prospective studies elucidate the relationship between maternal vitamin D and GDM and fetal growth, and obtain definitive conclusions.

REFERENCES

1. Liu NQ, Hewison M. Vitamin D, the placenta and pregnancy. Arch Biochem Biophys 2012;523:37-47.

2. Mulligan ML, Felton SK, Riek AE, et al. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol 2010;202:429.e1-9.

3. Dror DK, Allen LH. Vitamin D inadequacy in pregnancy: biology, outcomes, and interventions. Nutr Rev 2010;68:465-77.

4. Barrett H, McElduff A. Vitamin D and pregnancy: an old problem revisited. Best Pract Res Clin Endocrinol Metab 2010;24:527-39.

5. Joergensen JS, Lamont RF, Torloni MR. Vitamin D and gestational diabetes: an update. Curr Opin Clin Nutr Metab Care 2014;17:360-7.

6. Pittas AG, Lau J, Hu FB, et al. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017-29.

7. Weyer C, Bogardus C, Mott DM, et al. The natural history

of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104:787-94.

8. Hu FB, Meigs JB, Li TY, et al. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes 2004; 53:693-700.

9. Johnson DD, Wagner CL, Hulsey TC, et al. Vitamin D deficiency and insufficiency is common during pregnancy. Am J Perinatol 2011;28:7-12.

10. Wendland EM, Torloni MR, Falavigna M, et al. Gestational diabetes and pregnancy outcomes--a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth 2012;12:23.

11. Boyle VT, Thorstensen EB, Mourath D, et al. The relationship between 25-hydroxyvitamin D concentration in early pregnancy and pregnancy outcomes in a large, prospective cohort. Br J Nutr 2016;116:1409-15.

12. Park S, Yoon HK, Ryu HM, et al. Maternal vitamin D deficiency in early pregnancy is not associated with gestational diabetes mellitus development or pregnancy outcomes in Korean pregnant women in a prospective study. J Nutr Sci Vitaminol (Tokyo) 2014;60:269-75.

13. Tomedi LE, Simhan HN, Bodnar LM. Early-pregnancy maternal vitamin D status and maternal hyperglycaemia. Diabet Med 2013;30:1033-9.

14. Baker AM, Haeri S, Camargo CA, Jr., et al. First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study. Diabetes Metab Res Rev 2012;28:164-8.

15. Savvidou MD, Akolekar R, Samaha RB, et al. Maternal serum 25-hydroxyvitamin D levels at 11(+0) -13(+6) weeks in pregnant women with diabetes mellitus and in those with macrosomic neonates. BJOG 2011;118:951-5.

16. Makgoba M, Nelson SM, Savvidou M, et al. First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. Diabetes Care 2011;34: 1091-3.

17. Lacroix M, Battista MC, Doyon M, et al. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. Acta Diabetol 2014;51:609-16.

18. Zhang C, Qiu C, Hu FB, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabe-

tes mellitus. PLoS One 2008;3:e3753.

19. Poel YH, Hummel P, Lips P, et al. Vitamin D and gestational diabetes: a systematic review and meta-analysis. Eur J Intern Med 2012;23:465-9.

20. Aghajafari F, Nagulesapillai T, Ronksley PE, et al. 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.

21. Triunfo S, Lanzone A, Lindqvist PG. Low maternal circulating levels of vitamin D as potential determinant in the development of gestational diabetes mellitus. J Endocrinol Invest 2017. http://dx.doi.org/10.1007/s40618-017-0696-9.

22. Miliku K, Vinkhuyzen A, Blanken LM, et al. Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. Am J Clin Nutr 2016;103:1514-22.

23. Lee DH, Ryu HM, Han YJ, et al. Effects of serum 25-hydroxyvitamin D and fetal bone growth during pregnancy. J Bone Metab 2015;22:127-33.

24. Rodriguez A, Garcia-Esteban R, Basterretxea M, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG 2015; 122:1695-704.

25. Walsh JM, Kilbane M, McGowan CA, et al. Pregnancy in dark winters: implications for fetal bone growth? Fertil Steril 2013;99:206-11.

26. Young BE, McNanley TJ, Cooper EM, et al. Maternal vitamin D status and calcium intake interact to affect fetal skeletal growth in utero in pregnant adolescents. Am J Clin Nutr 2012;95:1103-12.

27. Ioannou C, Javaid MK, Mahon P, et al. The effect of maternal vitamin D concentration on fetal bone. J Clin Endocrinol Metab 2012;97:E2070-7.

28. Mahon P, Harvey N, Crozier S, et al. Low maternal vitamin D status and fetal bone development: cohort study. J Bone Miner Res 2010;25:14-9.

29. Galthen-Sorensen M, Andersen LB, Sperling L, et al. Maternal 25-hydroxyvitamin D level and fetal bone growth assessed by ultrasound: a systematic review. Ultrasound Obstet Gynecol 2014;44:633-40.

30. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2015;103:1278-88.e4.