International Journal of Gynaecology and Obstetrics Research
www.gynaecologyjournal.in
E-ISSN: 2663-3612, P-ISSN: 2663-3604
Received: 16-07-2021, Accepted: 02-08-2021, Published: 18-08-2021
Volume 3, Issue 2, 2021, Page No. 05-08

Effect of maternal vitamin D on fetal bone developemennt: Prospective study

Kalaiyarasi Umapathy M S[1*], N Hephzibah Kirubamani[2]
[1] Fellowship in Foetal Medicine Unit, Department of Obstetrics and Gynaecology, Saveetha Medical College and Hospital, Saveetha Nagar, Thandalam, Chennai, Tamil Nadu, India
[2] Chief, Foetal Medicine Unit, Department of Obstetrics and Gynaecology, Saveetha Medical College and Hospital, Saveetha Nagar, Thandalam, Chennai 602 105, Tamil Nadu, India

Abstract
In pregnancy, the women's physiology adapts to meet additional mineral demand of developing fetus. During third trimester the fetus actively transports minerals across the placenta to maintain high circulating levels to mineralize the actively developing skeleton. Hence the maternal vitamin D insufficiency affects fetal bone health. To investigate the effect of maternal serum level of vitamin D on fetal bone development, we studied 600 pregnant prospectively. With use of high resolution 3D ultrasound, we measured femoral length and femoral splaying index at 18-22 weeks of gestation and also at 32-34 weeks of gestation along with serum vitamin D3 level. Our study revealed that lower maternal vitamin D was not related to femur length but associated with higher splaying index at second and third trimester ultra-sonograms. We categorized the study women into three groups according to serum vitamin D concentration- borderline (>50nmol/L, 59.33%), insufficient (25nmol/L - 50nmol/L, 32,67%), deficient (<25nmol/L,8%). Among them, the mean femoral splaying index increases from 0.072 (sufficient/borderline) to 0.078 (insufficient) and 0.086 (deficient). Our study suggests that maternal vitamin D can influence the fetal bone health as early as 18-20 weeks, hence measurements to improve maternal vitamin D status should be instituted from early pregnancy onwards.

Keywords: vitamin D, fetal bone health, femoral splaying index

Introduction
During pregnancy, maternal vitamin D deficiency is very common and it causes significant public health issue [1]. In a study among pregnant women in northeast India [2], the prevalence was 93.3%. The risk factors include ethnicity, extensive skin covering, obesity, use of sunscreen, smoking and low dietary intake in addition to seasonal variation [3]. The fetus solely depends on maternal vitamin D which is transmitted via placenta [4], proved by maternal and cord blood vitamin D. Fig 1 shows the transport of active vitamin D (Cholecalciferol) across placenta.

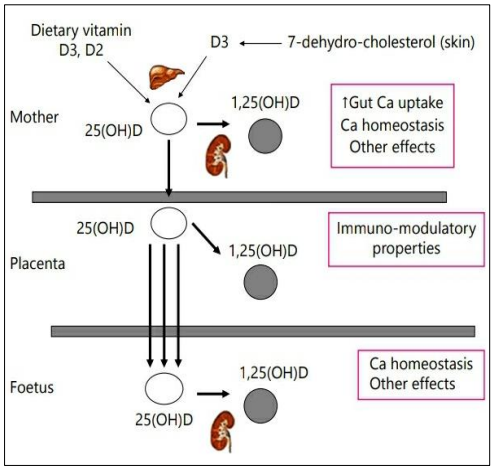

Fig 1: Maternal-fetal vitamin D transfer

Numerous mother-offspring cohort study showed that maternal vitamin D deficiency has direct consequence on fetal bone health [5, 6]. But only little information is available on the consequence of vitamin D deficiency on fetal bone health and at what gestational age it starts influencing. All these will be answered by measurement of femur length by 3D ultra-sonogram, which enables intrauterine bone evaluation and we measured femoral length and distal femoral metaphyseal cross-sectional area to derive femoral splaying index (ratio of femoral metaphyseal cross sectional area to femur length) [7], commonly used in childhood to measure rickets. The larger prevalence of vitamin D deficiency among adolescents and reproductive women will play negative role in fetal programming of next generation when they become pregnant [8]. Thus, it is important to measure maternal vitamin D levels for better fetal bone health.In this study we measured maternal serum vitamin D level and femur length, femoral splaying index to establish their inherit relationship and address them.

Materials and Methods
This is prospective observational analytical study conducted in the fetal medicine unit, Saveetha medical college hospital in 600 pregnant with gestational age 18 -22 weeks and followed at 32-34 weeks from August 2020 to May 2021 after getting informed consent. Along with routine investigations we did ultrasound examination of fetal thigh at 18-20 weeks and at 32-34weeks using Vinno G60 system fitted with curvilinear probe with

frequency ranging between 4-5Hz and a scan angle of 15-25^0. We took standard linear measurement of femur length and cross sectional area of distal femoral epiphysis to derive femoral splaying index as shown in fig 2.

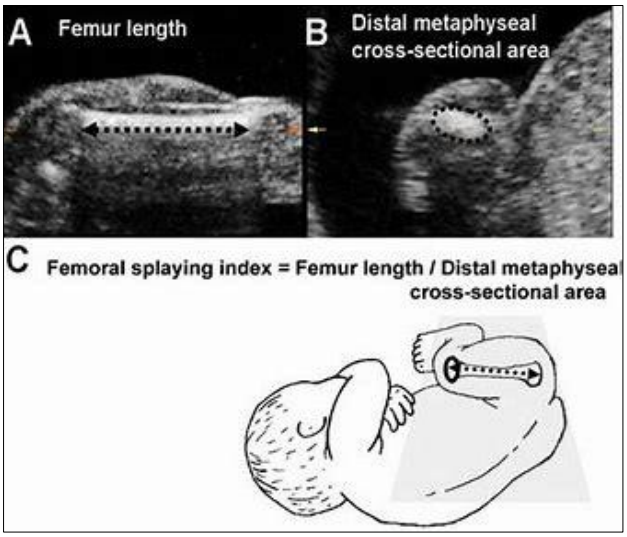

Fig 2: Multiplanar display of fetal thigh in 3D-USG

Each measurement was done 3 times and the mean value was considered.

Femoral shape was assessed by femoral splaying index, distal femoral metaphseal cross sectional area (cm^2) divided by femur length (cm).

This index assesses the degree of metaphyseal splaying in relation with femur length. During ultra-sonogram at 32 -34 weeks of gestation we also obtained 2ml of venous blood sample for measuring serum vitamin D level and categorized as sufficient(>70nmol/L); borderline (50-70nmol/L); insufficient (25-50nmol/L; deficient(<25nmol/L) according to 25-hydroxyvitamin D concentration [9]. The data collected was stored in investigative form and analysed using Stata Statistical Software Release 10,2008 software. We used Pearson's correlation co-efficient to find strength of observed value and their statistical significance. This study was approved by the Institutional Review Board of Saveetha Medical College Hospital and all the participants gave informed, written consent.

Result

600 antenatal mother recruited for the study. The mean age of participating mother is 24.3 years, mean maternal height was 162.6cm and 62.1% were primi gravida. Mean femur length is 3.12cm at 18-20week and 6.82cm at 32-34week gestation; corresponding mean distal femoral cross sectional area was 0.226cm^2 and 0.794cm^2, increased over the period of gestation. The mean femoral splaying index rose from 0.072 to 0.116cm^2/cm at 32-34 weeks gestation. The median maternal serum level of 25-OH vitamin D at 32-34 week gestation was 58.4nmol/L. Vitamin D concentration above 70nmol/L were present in 114 women (19%); a further 242 women (40.33%) had values falling between 50-70nmol/L (borderline); 196 women (32.67%- insufficient) values between 25-50nmol/L; remaining 48 women (8%) had value <25nmol/L (deficient) as shown in Fig 3.

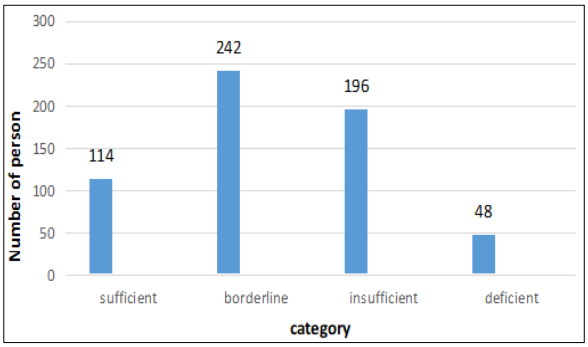

Fig 3: Maternal Vitamin D Level

At 18-20 weeks maternal vitamin D concentration was not related with femur length but lower level of vitamin D is associated with greater metaphyseal cross sectional area and femoral splaying index at 18-20 weeks of gestation. When compared with mothers having sufficient vitamin D, distal femoral metaphyseal cross sectional area was 6% more in mothers of insufficient group and 16% greater in mothers of deficient group. This trend followed in femoral shape too, assessed by femoral splaying index. When categorized the mean femoral splaying index at 18-20 week gestation is 0.072cm^2/cm in mothers with vitamin D >50nmol/L; in fetuses of insufficient and deficient the splaying index values were 0.076cm^2/cm and 0.086cm^2/cm respectively.

At 32-34 weeks also there was no association between femur length and maternal vitamin D level, but greater distal metaphyseal cross-sectional area, femoral splaying index was greater in deficient groups. This relationship is similar to observation at 18-20 weeks.

Discussion

This study reveals that low level of maternal serum vitamin D causes splaying of femur as early as 18-20 weeks. This distal femoral splaying index in fetuses of mother with low maternal vitamin D is analogue to index of childhood rickets, thus fetal femoral morphology could be a predictor of childhood rickets` [10, 11]. Neonatal vitamin D stores is completely dependent on mother, hence poor maternal vitamin D level is major risk factor for childhood rickets [12]. In-utero, or in early life vitamin D deficiency is linked to development of numerous pregnancy related complications like pre-eclampsia, preterm birth and in fetuses its deficiency causes impaired cognitive function, autism spectrum disorder, attention deficit hyperactivity disorder[13]. Therefore it is necessary to measure serum vitamin D level in early pregnancy or at pre-conception. Recent systematic review on role of maternal vitamin D in fetal bone health concludes that more studies are needed, despite some suggests that low maternal vitamin D levels affects bone length, especially if associated with low calcium intake [14, 15]. MAVIDOS study [16] found that gestational supplementation of vitamin D 1000IU/day has not improved fetal bone mass in summer, but greater mineral accretion during winter, proving that Vitamin D is homeostatic with calcium in fetal bone health. Observational studies found lower maternal vitamin D is at greater risk for pre-eclampsia, preterm birth, gestational diabetes, cesarean section, fetal growth restriction [17, 18]. Low serum level of maternal vitamin D in offspring exposes risk of asthma, impaired bone health, impaired neurodevelopmet and allergies [19-22]. Since vitamin D has

immunomodulatory effect its availability reduces incidence of pre-eclampsia. Strom *et al* [23] found higher association between low maternal vitamin D and attention deficit hyperactivity disorder, whereas higher have reduced incidence [24]. A study from china showed increased incidence of autism spectrum disorder in low maternal vitamin D [25].

Later life implication

Much data are available that altered bone development in early post natal and intrauterine life increases risk of fracture and osteoporosis in adult life [26]. May have low bone mass assessed by X-ray absorptiometry [27] and it is independent of environmental risk factors if associated with low maternal vitamin D [28].

Conclusion

In summary our study found that serum level of vitamin D during pregnancy influences fetal bone health as early as 18-20 week gestation.Hence large intervention studies must be done to determine appropriate level of vitamin D supplementation during pregnancy on maternal and perinatal outcomes. Screening for vitamin D as early or better at the preconceptional period must be done especially in obese women, dark skinned women, women on corticosteroid treatment, hypertension treatment, diabetes or auto-immune disease so that they can have appropriate treatment and better monitoring of pregnancy.

Acknowledgments

We thank mothers who gave us time and their relatives for their cooperation and their consent for publication of data in medical journal.

References

1. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev,2016:(1):CD008873. doi: 10.1002/14651858.CD008873.pub3. Update in: Cochrane Database Syst Rev. 2019 Jul 26;7:CD008873. PMID: 26765344.
2. G Ritu, Ajay Gupta. "Vitamin D deficiency in India: prevalence, causalities and interventions." Nutrients,2014:6(2):729-75. doi:10.3390/nu6020729
3. Rodda CP, Benson JE, Vincent AJ, Whitehead CL, Polykov A, Vollenhoven B. Maternal vitamin D supplementation during pregnancy prevents vitamin D deficiency in the newborn: an open-label randomized controlled trial. Clin Endocrinol (Oxf),2015:83(3):363-368.
4. Liu NQ, Hewison M. Vitamin D, the placenta and pregnancy. Arch Biochem Biophys,2012:523(1):37-47. doi: 10.1016/j.abb.2011.11.018. Epub 2011 Dec 2. PMID: 22155151.
5. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, Arden NK *et al*. Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet,2006:367(9504):36-43. doi: 10.1016/S0140-6736(06)67922-1. Erratum in: Lancet,2006:367(9521):1486. PMID: 16399151.
6. Harvey NC, Javaid MK, Poole JR, Taylor P, Robinson SM, Inskip HM *et al*. Southampton Women's Survey Study Group. Paternal skeletal size predicts intrauterine bone mineral accrual. J Clin Endocrinol Metab,2008:93(5):1676-81. doi: 10.1210/jc.2007-0279. Epub, 2008 Feb 19. PMID: 18285416.
7. Mahon P, Harvey N, Crozier S, Inskip H, Robinson S, Arden N *et al*. SWS Study Group. Low maternal vitamin D status and fetal bone development: cohort study. J Bone Miner Res,2010:25(1):14-9. doi: 10.1359/jbmr.090701. PMID: 19580464; PMCID: PMC4768344.
8. Larqué E, Morales E, Leis R, Blanco-Carnero JE. Maternal and Foetal Health Implications of Vitamin D Status during Pregnancy. Ann Nutr Metab,2018:72(3):179-192. doi: 10.1159/000487370. Epub 2018 Mar 13. PMID: 29533937.
9. Ruston D, Hoare J, Henderson L *et al* The National Diet and Nutrition Survey: adults aged 19 to 64 years. Nutritional status (anthropometry and blood analytes), blood pressure and physical activity. London: Stationery Office, 4, 20021-156.
10. Prentice A, Schoenmakers I, Laskey MA, de Bono S, Ginty F, Goldberg GR. Nutrition and bone growth and development. Proc Nutr Soc,2006:65(4):348-60. doi: 10.1017/s0029665106005192. PMID: 17181901; PMCID: PMC2039894.
11. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr,2004:80(6 Suppl):1678S-88S. doi: 10.1093/ajcn/80.6.1678S. PMID: 15585788.
12. Reif S, Katzir Y, Eisenberg Z, Weisman Y. Serum 25-hydroxyvitamin D levels in congenital craniotabes. Acta Paediatr Scand,1988:77(1):167-8. doi: 10.1111/j.1651-2227.1988.tb10620.x. PMID: 3369298.
13. McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Järvelin MR *et al*. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res,2004:67(2-3):237-45. doi: 10.1016/j.schres.2003.08.005. PMID: 14984883.
14. Galthen-Sørensen M, Andersen LB, Sperling L, Christesen HT. Maternal 25-hydroxyvitamin D level and fetal bone growth assessed by ultrasound: a systematic review. Ultrasound Obstet Gynecol,2014:44(6):633-40. doi: 10.1002/uog.13431.
15. Young BE, McNanley TJ, Cooper EM, McIntyre AW, Witter F, Harris ZL *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(5):1103-12. doi: 10.3945/ajcn.111.023861. Epub 2012 Apr 4. PMID: 22492380; PMCID: PMC3325835.
16. Cooper C, Harvey NC, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I *et al*. MAVIDOS Study Group. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. Lancet Diabetes Endocrinol,2016:4(5):393-402. doi: 10.1016/S2213-8587(16)00044-9. Epub 2016 Mar 2. PMID: 26944421; PMCID: PMC4843969.
17. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review

and meta-analysis. J Matern Fetal Neonatal Med,2013:26(9):889-99. doi: 10.3109/14767058.2013.765849. Epub 2013 Feb 11. PMID: 23311886.

18. Aghajafari F, Nagulesapillai T, Ronksley P E, Tough S C, Oâ€™Beirne M, Rabi D M *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 doi:10.1136/bmj.f1169 Aghajafari F, Nagulesapillai T, Ronksley P E, Tough S C, Oâ€™Beirne M, Rabi D M *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. doi:10.1136/bmj.f1169.
19. Morales E, Guxens M, Llop S, Rodríguez-Bernal CL, Tardón A, Riaño I *et al*. INMA Project. Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. Pediatrics,2012:130(4):e913-20. doi: 10.1542/peds.2011-3289. Epub 2012 Sep 17. PMID: 22987876.
20. Feng H, Xun P, Pike K, Wills AK, Chawes BL, Bisgaard H *et al*. In utero exposure to 25-hydroxyvitamin D and risk of childhood asthma, wheeze, and respiratory tract infections: A meta-analysis of birth cohort studies. J Allergy Clin Immunol,2017:139(5):1508-1517. doi: 10.1016/j.jaci.2016.06.065. Epub 2016 Sep 14. PMID: 27639938.
21. 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):485-93. doi: 10.1542/peds.2011-2644. Epub 2012 Feb 13. PMID: 22331333.
22. Song H, Yang L, Jia C. Maternal vitamin D status during pregnancy and risk of childhood asthma: A meta-analysis of prospective studies. Mol Nutr Food Res, 2017, 61(5). doi: 10.1002/mnfr.201600657. Epub 2017 Mar 21. PMID: 27981740.
23. Strøm M, Halldorsson TI, Hansen S, Granström C, Maslova E, Petersen SB *et al*. Vitamin D measured in maternal serum and offspring neurodevelopmental outcomes: a prospective study with long-term follow-up. Ann Nutr Metab,2014:64(3-4):254-61. doi: 10.1159/000365030. Epub 2014 Oct 2. PMID: 25300268.
24. Daraki V, Roumeliotaki T, Koutra K, Chalkiadaki G, Katrinaki M, Kyriklaki A *et al*. High maternal vitamin D levels in early pregnancy may protect against behavioral difficulties at preschool age: the Rhea mother-child cohort, Crete, Greece. Eur Child Adolesc Psychiatry,2018:27(1):79-88. doi: 10.1007/s00787-017-1023-x. Epub 2017 Jul 6. PMID: 28685401.
25. Chen J, Xin K, Wei J, Zhang K, Xiao H. Lower maternal serum 25(OH) D in first trimester associated with higher autism risk in Chinese offspring. J Psychosom Res,2016:89:98-101. doi: 10.1016/j.jpsychores.2016.08.013. Epub 2016 Aug 31. PMID: 27663117.
26. Harvey N, Cooper C. The developmental origins of osteoporotic fracture. J Br Menopause Soc,2004:10(1):14-5, 29. doi: 10.1258/136218004322986726. PMID: 15107206.
27. Yarbrough DE, Barrett-Connor E, Morton DJ. Birth weight as a predictor of adult bone mass in postmenopausal women: the Rancho Bernardo Study. Osteoporos Int,2000:11(7):626-30. doi: 10.1007/s001980070085. PMID: 11069198.
28. Yarbrough DE, Barrett-Connor E, Morton DJ. Birth weight as a predictor of adult bone mass in postmenopausal women: the Rancho Bernardo Study. Osteoporos Int,2000:11(7):626-30. doi: 10.1007/s001980070085. PMID: 11069198.