Vitamin D Deficiency During Pregnancy

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Abstract

Even though vitamin D deficiency during pregnancy has become an area of increased research interest, the function of vitamin D during pregnancy for both the mother and fetus remains largely undefined.

Our review aims to examine the role of vitamin D deficiency in the course and outcome of pregnancy.

Results: Many lines of evidence have shown an association between vitamin D deficiency and maternal and fetal complications during pregnancy.

In some recent publications, changes in vitamin D and vitamin D binding protein (VDBP) levels in cervicovaginal fluid have been discussed as biomarkers of vaginal inflammation and predictors of the risk of preterm birth, several weeks before delivery. There are contradictory reports regarding the role of vitamin D and the risk of preterm birth. Preterm amniotic fluid spillage and preterm birth are associated with vitamin D deficiency and the inflammatory response. Vitamin D deficiency is a risk factor for preeclampsia and increases the likelihood of cesarean section.

Conclusion

- Vitamin D deficiency during pregnancy is associated with complications of pregnancy and childbirth;

- Different opinions regarding the impact of vitamin D deficiency during pregnancy, require further research considering population characteristics.

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[1]საქართველოს დავით აღმაშენებლის სახელობის უნივერსიტეტი, [2]ივ.ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი

აბსტრაქტი

მიუხედავად იმისა, რომ D ვიტამინის დეფიციტი ორსულობის დროს, გახდა არაერთი კვლევის გაზრდილი ინტერესის სფერო, D ვიტამინის ფუნქცია ორსულობის დროს როგორც დედისთვის, ასევე ნაყოფისთვის ძირითადად განუსაზღვრელი რჩება.

ჩვენი მიმოხილვის მიზანია D ვიტამინის დეფიციტის როლის შესწავლა ორსულობის მიმდინარეობასა და გამოსავალზე.

შედეგები: არაერთმა მტკიცებულებამ გამოავლინა D ვიტამინის დეფიციტის კავშირი ორსულობის დროს დედისა და ნაყოფის გართულებებთან.

ზოგიერთ ბოლო პუბლიკაციაში D ვიტამინისა და D ვიტამინის დამაკავშირებელი პროტეინის (VDBP) დონის ცვლილებები ცერვიკოვაგინალურ სითხეში, განხილულია როგორც ვაგინალური ანთების ბიომარკერები და ნაადრევი მშობიარობის რისკის პრედიქტორები, მშობიარობამდე რამდენიმე კვირით ადრე. არსებობს წინააღმდეგობრივი ცნობები D ვიტამინის როლსა და ნაადრევი მშობიარობის რისკთან დაკავშირებით. სანაყოფე წყლბის ნაადრევი დაღვრა და ნაადრევი მშობიარობა დაკავშირებულია D ვიტამინის დეფიციტთან და ანთებით პასუხთან. D ვიტამინის დეფიციტი წარმოადგენს პრეკლამფსიის რისკ-ფაქტორს და ზრდის საკეისრო კვეთის ალბათობას.

დასკვნები

- D ვიტამინის ნაკლებობა ორსულობის პერიოდში დაკავშირებულია ორსულობისა და მშობიარობის გართულებებთან;
- აზრთა სხვადასხვაობა ორსულობის პერიოდში D ვიტამინის დეფიციტის ზემოქმედების შესახებ, რაც განაპირობებს შემდგომი კვლევების ჩატარების აუცილებლობას პოპულაციური თავისებურებების გათვალისწინებით.

Vitamin D deficiency, generally defined as a 25-hydroxyvitamin D (25(OH)D) concentration of less than 50 nmol/L, affects nearly half of the world's population. For most people, the primary source of vitamin D is exposure to mid-wavelength ultraviolet (UVB) radiation from the sun. In winter, 25(OH)D concentrations are maintained within 60%-80% of summer concentrations, due to a combination of recirculation of 25(OH)D stored in muscle cells and oral intake, as well as exposure to a certain amount of UVB spectrum. 25(OH)D concentrations are influenced by many factors related to solar UVB radiation, including skin pigmentation, solar zenith angle, atmospheric aerosols and clouds, time spent in the sun, exposed skin surface area, use of sunscreen, age, and body mass index. Cultural and lifestyle differences such as beauty standards, including high regard for fair skin in dark-skinned populations and the avoidance of wrinkles, occupation, clothing associated with religion, urban/rural living, and fear of developing skin cancer or melanoma [1].

The high prevalence of vitamin D (VD) deficiency worldwide is a matter of growing concern due to its potential negative impact on human health, including pregnant women and their offspring. In addition to its classical function (regulation of calcium and phosphate metabolism), its deficiency is associated with numerous adverse health effects. The classic consequences of VD deficiency in pregnancy and the newborn have been late-onset hypocalcemia and rickets. Furthermore, recent studies have linked VD deficiency to several

clinical conditions of fertility and pregnancy, such as preeclampsia, gestational diabetes, increased cesarean section rates, and preterm labor [2].

Even though vitamin D deficiency has become an area of increased research interest during pregnancy as more evidence has identified its association with maternal and fetal complications during pregnancy [3], the function of vitamin D during pregnancy for both the mother and fetus remains largely undefined.

Our review aims to examine the role of vitamin D deficiency on the course and outcome of pregnancy.

Methods:

A literature search was conducted in PubMed/MEDLINE, Web of Science, Google Scholar, and the Cochrane Library (The Cochrane Database of Systematic Reviews). The following keywords were used: "vitamin D", "cholecalciferol", "25(OH)D", "pregnancy", "gestation", and "pregnancy complications".

Inclusion criteria: Publications published between January 2014 and December 2024 contain scientific studies of various designs: prospective and retrospective observational studies, case-control studies, crossover studies, randomized clinical trials, and placebo-controlled studies.

Exclusion criteria: Studies conducted on animals or cell cultures or the full text or abstract of the publication are not freely available.

Results and Discussion

As we mentioned, the source of vitamin D is exposure to the sun (vitamin D is produced in the skin by exposure to the ultraviolet spectrum of sunlight) - this form of vitamin D is cholecalciferol or vitamin D3. It is worthy to say that certain foods can also be a source of vitamin D [4].

Vitamin D is formed in the skin from 7-dehydrocholesterol (7-DHC), hydroxylated first in the liver (and other tissues) to 25-hydroxyvitamin D (25OHD), then in the kidney (and other tissues) to 1,25 dihydroxyvitamin D (1,25(OH)2D), 25OHD and subsequent catabolism

to both the 1,25(OH) and 24 (and 23) hydroxy forms - 24,25(OH)2D and 1,24,25(OH)3D (or 1,23,25(OH)3D).

Vitamin D circulates bound to vitamin D binding protein (DBP), which is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D) and then in the kidney by 1 alpha-hydroxylase to 1-25 dihydroxyvitamin D (25(OH)2D3), is the active metabolite. There is also active vitamin D production in other organs. The vitamin D receptor (VDR), the enzyme 1 alpha-hydroxylase, and the production of 1-25(OH)2D3 have been shown in various tissues [5].

For dark-skinned people, sunlight is not as effective for vitamin D production, as the increased content of the skin pigment melanin reduces the production of 25(OH)D in the skin when exposed to ultraviolet rays [6,7].

Moreover, due to its classical effects on phospho-calcium homeostasis and bone health, vitamin D selectively regulates genes involved in cardiovascular processes, glucose metabolism, cell differentiation, and immunoregulation. Observational studies have shown an inverse relationship between 25(OH)D and disease incidence, but do not provide evidence of causality [8]. Additionally, to influence several pathologies, it has also been reported to affect allergic and autoimmune diseases and even cancer outcomes [9].

Certain research studies have shown an association between low serum 25(OH)-vitamin D levels during pregnancy and maternal/child health outcomes [10].

Even though there is modest evidence for an association between maternal 25(OH)D status and offspring birth weight, bone mass, and serum calcium concentration, the evidence base is currently insufficient to support specific clinical recommendations for vitamin D supplementation during pregnancy [10].

A review using 30 studies (23,760 participants) found that vitamin D was identified as a significant predictor of gestational diabetes [11.12]. A positive correlation between 25(OH) vitamin D concentration and insulin sensitivity and vitamin D deficiency has been identified, which may be a marker of insulin resistance [13,14].

Low maternal vitamin D concentrations in early pregnancy statistically improbably increase the risk of preterm birth [15].

During pregnancy, significant changes occur in phosphate and calcium metabolism due to the accumulation of calcium in the fetal skeleton. Fetal development and adequate bone mineralization depend solely on the mother's vitamin D stores, which she receives through the placenta since the fetus cannot synthesize vitamin D by itself. Low vitamin D levels during pregnancy are particularly concerning in early pregnancy, as they lead to a lack of bone mineral in the fetal skeleton. The concentration of calcitriol in fetal blood is lower than in maternal serum [16,17,18]. Since calcitriol does not readily cross the placental barrier [19], fetal parathyroid hormone concentrations are also low. High serum phosphorus and calcium concentrations also contribute to the reduction of fetal calcitriol concentrations because these factors suppress fetal renal 25OHD-1-α-hydroxylase (CYP27B1) expression [20].

Placental dysfunction can lead to miscarriage, premature birth, and stillbirth [21,22].

Vitamin D can also be called 25-hydroxyvitamin D or calcidiol, and it is converted to its active form 1,25-dihydroxyvitamin D by CYP27B1. This enzyme is primarily localized in the kidneys but is also significantly expressed in the placenta. Pregnancy is a special physiological state because the placenta plays an important role in the metabolism of this vitamin [23]. The placenta is considered the main site of vitamin D metabolism during pregnancy. Due to the pleiotropic properties of the vitamin D receptor (VDR), growing scientific evidence points to the role of vitamin D in maternal mortality and morbidity [24].

An inverse correlation was observed between cord blood 25(OH)D levels at birth and neonatal weight [25], while other studies have shown that infants of mothers with severe vitamin D deficiency have shorter birth length, smaller head circumference, and smaller birth weight [26].

There is contrary evidence regarding the role of vitamin D and the risk of preterm birth. Preterm premature rupture of membranes and preterm birth have been associated with vitamin D deficiency and inflammatory response [27], with low maternal serum vitamin D levels associated with an approximately nine-fold increased risk of preterm birth compared with normal vitamin D levels [28]. However, other studies have not demonstrated an association between 25(OH)D status and preterm birth [29,30].

According to some studies, vitamin D deficiency in early and late pregnancy may not be associated with PTB. As for vitamin D, its deficiency in the second trimester of pregnancy may have a significant impact on PTB. Therefore, vitamin D levels should be measured in the second trimester of pregnancy and vitamin D supplements should be given if necessary [31].

Several recent publications have discussed changes in vitamin D and vitamin D binding protein (VDBP) levels in cervicovaginal fluid as biomarkers of vaginal inflammation and predictors of the risk of preterm labor in the weeks before delivery [32]. Follow-up studies of vitamin D supplementation and preterm delivery should include cervical vaginal VDBP and serum 1,25(OH)2D as well as 25(OH)D to monitor response to vitamin D supplementation and preeclampsia.

Clinical and epidemiological evidence regarding the association between low maternal vitamin D levels and the risk of preeclampsia is inconsistent [33].

Preeclampsia is a pregnancy-specific condition characterized by endothelial dysfunction and vasospasm that typically occurs after 20 weeks of gestation. It is clinically defined by the onset of hypertension, with or without proteinuria, with or without severe symptoms [34].

Preeclampsia and its complications are responsible for 63,000 maternal deaths worldwide each year, accounting for 12% of maternal mortality [35].

The pathogenesis of preeclampsia is not fully understood; however, its development may be due to a complex interaction of ischemia and abnormal placentation. Since maternal vitamin D deficiency is associated with an increased risk of cardiovascular disease and hypertension, it is likely that vitamin D supplementation may play a protective role in the treatment of preeclampsia by promoting endothelial health and regulating blood pressure [36].

Baker and his colleagues in their study reported that in the United States, women with vitamin D levels <20 ng/mL had a 4-fold increased risk of severe preeclampsia. Additionally, women with early severe preeclampsia and small-for-gestational-age (SGA) infants had significantly lower vitamin D levels than infants with severe preeclampsia, but not small-for-gestational-age infants [37]. This is further supported by a 2023 Swedish case-control study that identified vitamin D deficiency as a risk factor for preeclampsia [38] - suggesting that

vitamin D supplementation during pregnancy significantly reduces the risk of preeclampsia and preterm birth [39].

Maternal vitamin D levels in the first trimester were positively associated with fetal growth in length and were not associated with weight or head circumference. A correlation was observed between a higher risk of preterm birth and a longer average gestational age. Second-trimester vitamin D status was not associated with fetal growth or pregnancy outcomes. Based on this study, it is likely that the first trimester may be a critical time for intervention in women with vitamin D deficiency [40]. However, a population-based prospective cohort study of 7098 pregnant women in the Netherlands reported an association between maternal vitamin D levels in the second trimester and fetal weight and head circumference growth [41].

According to a study conducted in Singapore, only 2.2% of the female population had sufficient levels of vitamin D. However, the higher the body mass index, the greater the likelihood of vitamin D deficiency. It should be highlighted that the older the patient, the less likely they are to be deficient [42].

Low vitamin D levels are associated with glucose homeostasis [43], excessive weight gain during pregnancy contributes to the risk of gestational diabetes, and low maternal vitamin D levels are associated with low maternal vitamin D levels because the vitamin is fat-soluble and moves from the blood into adipose tissue [44]. Furthermore, obesity in patients with vitamin D deficiency is associated with a reduced fraction of bioactive, unbound 15(OH)D [45].

There are contradictory data regarding the association of maternal vitamin D levels with preterm birth and small for gestational age (SGA) fetuses [46,47]. In a recent systematic review supporting the Endocrine Society's recommendations for vitamin D for pregnant women, the authors concluded that vitamin D supplementation may have "significant potential benefits" on the risk of SGA and preterm birth [48]. A systematic review and meta-analysis confirmed the well-documented effect of maternal vitamin D supplementation on newborn size [49].

Low blood 25(OH)D levels are associated with a higher rate of cesarean section, and vitamin D deficiency in pregnant women during labor may affect labor progression both

directly and indirectly through maternal complications such as preeclampsia and preterm labor, and may lead to a higher likelihood of cesarean section [50]. A randomized controlled trial conducted in Iran found that calcium and vitamin D3 significantly reduced the rate of cesarean section in women who developed gestational diabetes (23 vs 63%, p = 0.002). A study of vitamin D supplements found that taking at least 50,000 IU of vitamin D3 per month significantly reduced the risk of preeclampsia and gestational diabetes in women with vitamin D deficiency [51].

Taking vitamin D supplements during pregnancy increases birth weight and reduces the risk of maternal preeclampsia [52,53], spontaneous abortion and vitamin D deficiency, fetal or neonatal mortality, and attention deficit hyperactivity disorder and autism spectrum disorder in childhood. In women with gestational diabetes, vitamin D supplementation during pregnancy may reduce the risk of maternal hyperbilirubinemia, polyhydramnios, macrosomia, fetal distress, and neonatal hospitalization [54].

Taking vitamin D during pregnancy at a dose of 2000 IU or more is a preventive measure against the development of preeclampsia, insulin resistance and bronchial asthma in early childhood. Vitamin D screening is indicated for all pregnant women. Doses of vitamin D supplements should be determined individually, taking into account laboratory tests and risk factors [55].

High maternal 25(OH)D levels prior to intervention are associated with reduced risk of autism [56].

Therefore, the authors agree that in cases of vitamin D deficiency during pregnancy, vitamin D supplementation is recommended. However, further research is needed to better define the risks, benefits, and potential public health impacts associated with such interventions.

Conclusion

- Vitamin D deficiency during pregnancy is associated with complications during pregnancy and childbirth;

- There are different opinions regarding the impact of vitamin D deficiency during pregnancy, which requires further research considering the characteristics of the population.

ლიტერატურა

1. Grant WB, Bhattoa HP, Pludowski P. Determinants of vitamin D levels from sun exposure: a global perspective. InFeldman and Pike's Vitamin D 2024 Jan 1 (pp. 97-113). Academic Press.
2. Mansur JL, Oliveri B, Giacoia E, Fusaro D, Costanzo PR. Vitamin D: before, during and after pregnancy: effect on neonates and children. Nutrients. 2022 May 1;14(9):1900.
3. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. The Journal of Clinical Endocrinology & Metabolism. 2007 Sep 1;92(9):3517-22.
4. Liberman U, Bikle DD. Disorders in the Action of Vitamin D. 2023 Jul 6. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 25905373.
5. Bikle DD. Vitamin D: Newer concepts of its metabolism and function at the basic and clinical level. Journal of the Endocrine Society. 2020 Feb;4(2):bvz038.
6. Singh Ospina N, Diaz-Thomas A, McDonnell ME, Demay MB, Pittas AG, York E, Corrigan MD, Lash RW, Brito JP, Murad MH, McCartney CR. Navigating complexities: vitamin D, skin pigmentation, and race. The Journal of Clinical Endocrinology & Metabolism. 2024 Jun 3:dgae314.
7. iaz-Thomas A, McDonnell ME, Demay MB, Pittas AG, York E, Corrigan MD, Lash RW, Brito JP, Murad MH, McCartney CR. Navigating Complexities: Vitamin D, Skin Pigmentation, and Race. The Journal of Clinical Endocrinology and Metabolism. 2024 Jun 3:dgae314-.
8. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, Lips P, Munns CF, Lazaretti-Castro M, Giustina A, Bilezikian J. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocrine reviews. 2019 Aug;40(4):1109-51.
9. Marino R, Misra M. Extra-skeletal effects of vitamin D. Nutrients. 2019 Jun 27;11(7):1460.

10. Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R, Cole Z, Tinati T, Godfrey K, Dennison E, Bishop NJ. Vitamin D supplementation in pregnancy: a systematic review. Health technology assessment (Winchester, England). 2014 Jul 1;18(45):1-90.
11. Abera DA, Larbie C, Abugri J, Ofosu M, Mutocheluh M, Dongsogo J. Prevalence and Predictors of Gestational Diabetes Mellitus in Sub-Saharan Africa: A 10-Year Systematic Review. Endocrinol Diabetes Metab. 2024 May;7(3):e00478.
12. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, Shoenfeld Y, Lerchbaum E, Llewellyn DJ, Kienreich K, Soni M. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—a review of recent evidence. Autoimmunity reviews. 2013 Aug 1;12(10):976-89.
13. Rafiq S, Jeppesen PB. Vitamin D Deficiency Is Inversely Associated with Homeostatic Model Assessment of Insulin Resistance. Nutrients. 2021 Dec 3;13(12):4358.
14. Nisar M, Beigh SA, Mir AQ, Hussain SA, Dar AA, Yatoo I, Khan AM. Association of vitamin D status with redox balance and insulin resistance and its predicting ability for subclinical pregnancy toxemia in pregnant sheep. Domestic Animal Endocrinology. 2024 Jan 1;86:106823.
15. Olstrup H, Rylander L, Lindh C, Malm G, Vilhelmsson A. Maternal Serum Concentrations of Vitamin D Early in Pregnancy and Preterm Birth: A Case-Control Study in Southern Sweden.2023.

16. Barrera D, Díaz L, Noyola-Martínez N, Halhali A. Vitamin D and inflammatory cytokines in healthy and preeclamptic pregnancies. Nutrients. 2015 Aug 4;7(8):6465-90.
17. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017 Jun;18(2):153-165. doi: 10.1007/s11154-017-9424-1. PMID: 28516265.
18. Varsavsky M, Moreno PR, Fernández AB, Fernández IL, Gómez JM, Rubio VÁ, Martín AG, Berdonces MC, Cortés SN, Muñoz MR, García RR. Recommended vitamin D levels in the general population. Endocrinología, Diabetes y Nutrición (English ed.). 2017 Mar 1;64:7-14.
19. O'Brien, K.O., Li, S., Cao, C., Kent, T., Young, B.V., Queenan, R.A., Pressman, E.K. and Cooper, E.M., 2014. Placental CYP27B1 and CYP24A1 expression in human placental tissue and their association with maternal and neonatal calcitropic hormones. *The Journal of Clinical Endocrinology & Metabolism*, *99*(4), pp.1348-1356.
20. Suárez-Varela MM, Uçar N, Peraita-Costa I, Huertas MF, Soriano JM, Llopis-Morales A, Grant WB. Vitamin D-Related Risk Factors for Maternal Morbidity during Pregnancy: A Systematic Review. Nutrients. 2022 Jul 31;14(15):3166.

21. Makharadze M, Sulukhia R, Tsiklauri M, Melia L, Taboridze I. Risk Factors for Spontaneous Abortion in Georgian Population. European Scientific Journal.2019;15 (33): e 1857- 7431.
22. Makharadze M, Sulukhia R, Megrelishvili N, Melia L, Taboridze I. Correlations between spontaneous abortions and patient's history, social-biological and environmental factors. Experimental and Clinical Medicine Georgia. 2019(2):17-9.
23. Tamblyn JA, Hewison M, Wagner CL, Bulmer JN, Kilby MD. Immunological role of vitamin D at the maternal–fetal interface. Journal of Endocrinology. 2015 Mar 1;224(3):R107-21.
24. Aguilar-Cordero MJ, Lasserrot-Cuadrado A, Mur-Villar N, León-Ríos XA, Rivero-Blanco T, Pérez-Castillo IM. Vitamin D, preeclampsia and prematurity: A systematic review and meta-analysis of observational and interventional studies. Midwifery. 2020 Aug 1;87:102707.
25. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. Journal of bone and mineral research. 2011 Oct 1;26(10):2341-57.
26. Song SJ, Si S, Liu J, Chen X, Zhou L, Jia G, Liu G, Niu Y, Wu J, Zhang W, Zhang J. Vitamin D status in Chinese pregnant women and their newborns in Beijing and their relationships to birth size. Public health nutrition. 2013 Apr;16(4):687-92.
27. Thota C, Menon R, Fortunato SJ, Brou L, Lee JE, Al-Hendy A. 1, 25-Dihydroxyvitamin D deficiency is associated with preterm birth in African American and Caucasian women. Reproductive Sciences. 2014 Feb;21(2):244-50.
28. Oluwole AA, Okunade KS, Okojie OE. Maternal serum vitamin D levels and preterm delivery among low-risk parturients in Lagos, Nigeria. International Journal of Gynecology & Obstetrics. 2019 Feb;144(2):216-20.
29. You Z, Mei H, Zhang Y, Song D, Zhang Y, Liu C. The effect of vitamin D deficiency during pregnancy on adverse birth outcomes in neonates: a systematic review and meta-analysis. Frontiers in Pediatrics. 2024 May 14;12:1399615.
30. Bhupornvivat N, Phupong V. Serum 25-hydroxyvitamin D in pregnant women during preterm labor. Asia Pacific journal of clinical nutrition. 2017 Jan;26(2):287-90.
31. Lian RH, Qi PA, Yuan T, Yan PJ, Qiu WW, Wei Y, Hu YG, Yang KH, Yi B. Systematic review and meta-analysis of vitamin D deficiency in different pregnancy on preterm birth: Deficiency in middle pregnancy might be at risk. Medicine. 2021 Jun 18;100(24):e26303.
32. Kook SY, Park KH, Jang JA, Kim YM, Park H, Jeon SJ. Vitamin D-binding protein in cervicovaginal fluid as a non-invasive predictor of intra-amniotic infection and impending preterm delivery in women with preterm labor or preterm premature rupture of membranes. PLoS One. 2018 Jun 7;13(6):e0198842.

33. Alimoradi Z, Kazemi F, Tiznobeik A, Griffiths MD, Masoumi SZ, Aghababaei S. The effect of vitamin D supplementation in pregnancy on the incidence of preeclampsia: A systematic review and meta-analysis. European Journal of Integrative Medicine. 2024 Feb 10:102343.
34. Chang K-J, Seow K-M, Chen K-H, Preeclampsia. Recent advances in Predicting, preventing, and managing the maternal and fetal life-threatening Condition. Int J Environ Res Public Health. 2023;20(4)
35. Villa, P.M., Kajantie, E., Räikkönen, K., Pesonen, A.K., Hämäläinen, E., Vainio, M., Taipale, P., Laivuori, H. and Predo Study group, 2013. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. *BJOG: An International Journal of Obstetrics & Gynaecology*, *120*(1), pp.64-74.
36. Hu K-L, Zhang C-X, Chen P, Zhang D, Hunt S. Vitamin D levels in early and middle pregnancy and Preeclampsia, a systematic review and Meta-analysis. Nutrients. 2022;14(5)
37. Robinson CJ, Wagner CL, Hollis BW, Baatz JE, Johnson DD. Maternal vitamin D and fetal growth in early-onset severe preeclampsia. American journal of obstetrics and gynecology. 2011 Jun 1;204(6):556-e1.
38. Malm G, Lindh CH, Hansson SR, Källén K, Malm J, Rylander L. Maternal serum vitamin D level in early pregnancy and risk for preeclampsia: A case-control study in Southern Sweden. Plos one. 2023 Feb 7;18(2):e0281234.
39. Moghib K, Ghanm TI, Abunamoos A, Rajabi M, Moawad SM, Mohsen A, Kasem S, Elsayed K, Sayed M, Dawoud AI, Salomon I. Efficacy of vitamin D supplementation on the incidence of preeclampsia: a systematic review and meta-analysis. BMC Pregnancy and Childbirth. 2024 Dec 23;24(1):852.
40. Beck C, Blue NR, Silver RM, Na M, Grobman WA, Steller J, Parry S, Scifres C, Gernand AD. Maternal vitamin D status, fetal growth patterns, and adverse pregnancy outcomes in a multisite prospective pregnancy cohort. The American Journal of Clinical Nutrition. 2024 Nov 20.
41. Miliku K, Vinkhuyzen A, Blanken LM, McGrath JJ, Eyles DW, Burne TH, Hofman A, Tiemeier H, Steegers EA, Gaillard R, Jaddoe VW. Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. The American journal of clinical nutrition. 2016 Jun 1;103(6):1514-22.
42. Amelia CZ, Gwan CH, Qi TS, Seng JTC. Prevalence of vitamin D insufficiency in early pregnancies- a Singapore study. PLoS One. 2024 Apr 11;19(4):e0300063.
43. Knabl J, Hüttenbrenner R, Hutter S, Günthner-Biller M, Riedel C, Hiden U, Kainer F, Desoye G, Jeschke U. Gestational diabetes mellitus upregulates vitamin D receptor in

extravillous trophoblasts and fetoplacental endothelial cells. Reproductive Sciences. 2015 Mar;22(3):358-66.

44. Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejnmark L, Richelsen B, Pedersen SB. Expression of vitamin D-metabolizing enzymes in human adipose tissue—the effect of obesity and diet-induced weight loss. International journal of obesity. 2013 May;37(5):651-7.
45. Hyppönen E, Boucher BJ. Adiposity, vitamin D requirements, and clinical implications for obesity-related metabolic abnormalities. Nutrition Reviews. 2018 Sep 1;76(9):678-92.
46. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane database of systematic reviews. 2016(1).
47. Agarwal S, Kovilam O, Agrawal DK. Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review. Critical reviews in food science and nutrition. 2018 Mar 24;58(5):755-69.
48. Shah VP, Nayfeh T, Alsawaf Y, Saadi S, Farah M, Zhu Y, Firwana M, Seisa M, Wang Z, Scragg R, Kiely ME. A systematic review supporting the endocrine society clinical practice guidelines on vitamin D. The Journal of Clinical Endocrinology & Metabolism. 2024 Jun 3:dgae312.
49. Maugeri A, Barchitta M, Blanco I, Agodi A. Effects of Vitamin D Supplementation During Pregnancy on Birth Size: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2019 Feb 20;11(2):442.
50. Amiri M, Rostami M, Sheidaei A, Fallahzadeh A, Ramezani Tehrani F. Mode of delivery and maternal vitamin D deficiency: an optimized intelligent Bayesian network algorithm analysis of a stratified randomized controlled field trial. Scientific Reports. 2023 May 29;13(1):8682.
51. Grant WB. Vitamin D Status May Help Explain Maternal Race and Ethnic Factors in Primary Cesarean Section Delivery. Am J Perinatol. 2021 Aug;38(S 01):e367-e369.
52. Xiaomang J, Yanling W. Effect of vitamin D3 supplementation during pregnancy on high risk factors—A randomized controlled trial. Journal of perinatal medicine. 2021 May 26;49(4):480-4.
53. Fogacci S, Fogacci F, Banach M, Michos ED, Hernandez AV, Lip GY, Blaha MJ, Toth PP, Borghi C, Cicero AF, Lipid and Blood Pressure Meta-analysis Collaboration. Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials. Clinical Nutrition. 2020 Jun 1;39(6):1742-52.

54. Chien MC, Huang CY, Wang JH, Shih CL, Wu P. Effects of vitamin D in pregnancy on maternal and offspring health-related outcomes: An umbrella review of systematic review and meta-analyses. Nutrition & Diabetes. 2024 May 30;14(1):35.
55. Kurmangali Z, Abdykalykova B, Kurmangali A, Zhantagulov D, Terzic M. The influence of vitamin D on pregnancy and outcomes: Current knowledge and future perspectives. Gynecologic and Obstetric Investigation. 2024 Mar 8:1-6.
56. Aagaard K, Jepsen JR, Sevelsted A, Horner D, Vinding R, Rosenberg JB, Brustad N, Eliasen A, Mohammadzadeh P, Følsgaard N, Hernández-Lorca M. High-dose vitamin D3 supplementation in pregnancy and risk of neurodevelopmental disorders in the children at age 10: A randomized clinical trial. The American journal of clinical nutrition. 2024 Feb 1;119(2):362-70.