Rickets in Offspring Delivered to Vitamin D Deficient Mother: A Review of Literatures

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(Ann Coll Med Mosul 2023; 45 (2):237-246).
Received: 24th May 2023; Accepted: 9th July 2023.

ABSTRACT

Vitamin D is essential nutrients for health. Both pregnant women and children and are more prone to have vitamin D deficiency and can cause nutritional rickets and disorders in calcium homeostasis. Many researches have connected vitamin D deficiency to negative health outcomes, including those that go beyond bone health, in both children and pregnant women. Reports of high incidence of nutritional rickets continue to progress. With adequate vitamin D and calcium supplementation, nutritional rickets is a completely avoidable illness that may be eradicated in infants and children around the world. In order to execute workable prevention measures for vitamin D insufficiency and nutritional rickets, a comprehensive, multi-level approach is required. The history, danger signs, and debates around vitamin D insufficiency during pregnancy and children are highlighted in this overview

Keywords: Rickets , vitamin D , mother , child .

الكساح عند الاطفال المولودين حديثا لأمهات مصابات بنقص فيتامين دال: مراجعة مقالة

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الخلاصة

يعتبر فيتامين دال من العناصر الغذائية الأساسية للصحة لكل من النساء الحوامل والأطفال الذين هم اكثر عرضة للإصابة بنقص فيتامين دال ويمكن أن يسبب كساحًا غذائيًا واضطرابات في استتباب الكالسيوم. ربطت العديد من الأبحاث نقص فيتامين دال بالنتائج الصحية السلبية ، بما في ذلك تلك التي تتجاوز صحة العظام في كل من الأطفال والنساء الحوامل. تستمر التقارير عن ارتفاع معدل الإصابة بالكساح الغذائي في التقدم. مع وجود مكملات غذائية مناسبة من فيتامين دال والكالسيوم ، يعد الكساح الغذائي مرضًا يمكن تجنبه تمامًا ويمكن القضاء عليه عند الرضع والأطفال في جميع أنحاء العالم . من أجل تنفيذ تدابير وقائية عملية لنقص فيتامين دال والكساح الغذائي ، يلزم اتباع نهج شامل متعدد المستويات. يتم تسليط الضوء على التاريخ وعلامات الخطر والمناقشات حول نقص فيتامين دال أثناء الحمل والأطفال في هذه النظرة العامة.

الكلمات المفتاحية : الكساح ، فيتامين دال ، الاطفال ، الأمهات .

INTRODUCTION

Nutritional rickets has a significant influence on young children's health, and development, and is caused by widespread vitamin D deficiency. Breastfed infants are more likely to suffer from vitamin D deficiency or insufficiency because of the low vitamin D levels in lactation. [1]

Numerous scientific investigations have investigated the effects of vitamin D supplementation during pregnancy and have produced conflicting results regarding the best time and dose to take it. [2] As it controls the metabolism of bones and minerals and can prevent and treat nutritional rickets and osteomalacia, vitamin D is necessary for the health of the musculoskeletal system. Several experimental and epidemiological studies also support the idea that vitamin D has a wider role in overall health since the vitamin D receptor (VDR) is expressed in practically all human cells. [3] .

Supplementation during pregnancy is an important subject in literature since vitamin D insufficiency is common among pregnant women worldwide. [4]

The fat-soluble vitamin D promotes calcium, phosphate, and magnesium absorption. It is utilized by the body to create calcified tissues and aids in preventing rickets. [5.] Rickets was regarded as the 'tip of the iceberg' for vitamin D insufficiency because of how crucial it is to human health. [6.] Additionally, a lack of vitamin D results in fetal and childhood growth retardation as well as bone abnormalities that aggravate osteopenia, osteoporosis, and the risk of fracture. [7.] In addition to helping to mineralize bones, vitamin D and calcium have a number of additional health advantages, including as improving immunity and reducing the risk of cancer, hypertension, diabetes, and autoimmune illnesses. [8.] The receptor for vitamin D, a steroid hormone, is found inside the nucleus and interacts with particular sequences of DNA to form a complex. Growth hormone and insulin-like growth factor-1 are two examples of the many growth-promoting proteins whose transcription is induced by vitamin D. [8-11.] There is debate over whether serum vitamin D levels should be adequate or ideal to prevent negative health effects. A blood concentration of more than 50 (nmol/L) (20 (ng/ml) of vitamin D during pregnancy was deemed appropriate by the US Institute of Medicine. [12]

Diet, geographic latitude, supplement use, cultural and lifestyle influences, and skin pigmentation are significant contributors, even though vitamin D insufficiency affects everyone at all levels. Vitamin D insufficiency is especially dangerous for young children, the elderly, pregnant and nursing women, and people with certain diseases including cancer. [13-16]

This narrative review's objective is to discuss the significance of vitamin D during pregnancy and childhood, the risk factors for vitamin D deficiency, the related clinical picture, particularly in the pediatric population, as well as the various prevention and therapy regimens that have been suggested. Additionally, rickets is covered. Up until January 2023, articles were found in PubMed searches by concentrating on the most pertinent studies.

Rickets

Rickets is a pediatric disease that causes clinical abnormalities in weight-bearing bones and metaphyseal plates anterior to epiphyseal fusion due to inadequate mineralization of the organic bone matrix and diminished apoptosis of endochondral columnar cartilage. Rickets is a condition that affects the growth plate cartilage and is most common in newborns and young children. This happens because the osteoid does not properly mineralize as a result of hypocalcemia or hypophosphatemia, or because minerals like fluoride and aluminum directly hinder the mineralization process. [17,18]

Endochondral ossification, in which extracellular matrix production in the hypertrophic chondrocytes at the ossification center will be mineralized in the presence of sufficient phosphate and calcium, is the process by which osseous tissue is produced from cartilage in growing long bones. Calcified cartilage is then reabsorbed, and then lamellar bone eventually replaces it. [19.] Chondrocyte apoptosis, which is the first step in the ossification process, is triggered by the extracellular phosphate-mediated phosphorylation of MAPK pathway intermediates. [20.] Low serum calcium prevents chondrocyte death as a result of compensatory hyperparathyroidism and subsequent hypophosphataemia. [21,22]

Due to the buildup of hypertrophic chondrocytes caused by this, the cartilaginous epiphyseal plate finally grows abnormally, and osteoid deposits under the growth plate. [17,18] In the end, this results in the phenotypical alterations and clinical symptoms of rickets, such as bone abnormalities, delay of development, and a high risk of hypo-calcaemic seizures,cardiomyopathy (in babies), and even death. [22] According to Munns et al.'s review, the diagnosis of rickets is frequently done by using a combination of clinical, radiological, and biochemical principles. [23]

Rickets can result from several aetiologies, including metabolic acquired deficiencies and minerals impairments due to problems in the renal tubular cells brought on by drugs like tetracycline and conditions like Fanconi's anemia. Direct gene mutations of genes related to bone homeostasis, mineralization, and renal metabolism are also among the causes of rickets. [24,25] Even though they are significant, these aetiologies are further discussed in other review articles. [17-19] The most frequent cause of rickets worldwide is secondary to dietary inadequacies, which are generally brought on by inadequate calcium, vitamin D, and/or phosphate intake. Various high-income nations, including the UK and Ireland (0.48 cases per 100,000) and Canada (2.9 cases per 100,000), have comparatively low incidences of nutritional

rickets. [26,27]. However, it appears that nutrient rickets is more prevalent in poor-income nations in Asia and Africa. For instance, radiography estimates that there are 2.7 instances per one thousand children in India, and clinical examination reports a prevalence of 3.3% in Gambian children. [28,29] Although some inter-study heterogeneity can be recognized in different diagnostic approaches (such as clinical, radiographic, and biochemical diagnoses), it is also plausible that subpopulations with a higher prevalence of rickets were chosen for investigation. [30]

Vitamin D Physiology

The skin begins to produce vitamin D after acquaintance to sunlight,, where vitamin D3 is created from 7dehydrocholesterol. Vitamin D2 and D3 can also be added to food, although they don't contribute nearly as much as endogenous synthesis does. [31,32] These substances are hydroxylated in the liver to produce 25(OH)D, which is then transformed by 1-alpha-hydroxylasis in the kidney to 1,25(OH)2 D. The placenta, among other tissues and organs, may actually experience the final hydroxylation reaction. [33] The active form of vitamin D is 1,25(OH)2 D, which binds to vitamin D receptors (VDRs) in target cells' nuclei and plasma membranes. [34] In order to explain calcium and absorption of phosphorus by the intestinal wall, reabsorption of calcium from the kidney's ultrafiltrate, activation of pre-osteoclasts into active osteoclasts in bone turnover, and parahormone negative feedback regulation. 1,25(OH)2 D's classic genomic effects are involved. In addition to bone metabolism, vitamin D has recently been linked to a number of other novel functions. At least 37 different tissue types exhibit VDRs. [33] Recently about 291 genes in vivo has been shown to be regulated up by vitamin D [35] , this will in favor of pleiotropic effects, including how vitamin D affects the immune system, muscles, and the heart.

The function of immunomodulation of vitamin D is of special relevance because these effects have been linked to a number of autoimmune diseases and help to trigger innate immune responses while disarming the adaptive immune system. [36] Numerous modifications to the mother's vitamin D metabolism take place during pregnancy as a result of the fetus' complete reliance on placental delivery and, consequently, on the mother's consumption and manufacture of the vitamin. [37]

Besides the kidney, the placenta also produces more vitamin D. [38] However, 25 hydroxy vitamin D go into fetal circulation and is hydroxylated into the equivalent active form in the fetal kidney, whereas 1,25(OH)2 D is unable to cross the placenta. [39] These alterations in the mothers and their fetus have typically been explained as a reaction to the fetal need for calcium. Given the extensive distribution of VDRs throughout the body and the numerous extraskeletal effects of vitamin D, it has been hypothesized that the physiologically elevated levels of 1,25(OH)2 D during pregnancy may control various other biological processes. [38] Over the years, there has been a large number of discussions over the need for optimal vitamin D levels. Aside from the controversy surrounding the usage of various 25(OH)D dosage techniques and the issue of inter-assay discrepancy [38,39] , On the thresholds that should be used to identify vitamin D sufficiency or deficient, there is currently no agreement. The threshold for vitamin D adequacy is determined by the Institute of Medicine (IOM) at a blood level of 20 ng/ml. [40,41] The Endocrine Society classifies non-pregnant women's hormone levels into three groups: deficiency (20 ng/ml), insufficiency (21–29 ng/ml), and sufficiency (> 30 ng/ml)[42] The classification for vitamin D levels in pregnant women is the same. Between 18 and 84% of women have hypovitaminosis D, depending on their ancestry and standard of living. [43] Recent studies in developed countries a prevalence of levels < 30 ng/ml of 10-30% in pregnant women has been reported. [44] Screening pregnant women who carry high risk for low vitamin D to make sure their serum 25(OH)D level is greater than 30 ng/ml seems to be a suitable practice. Season, latitude, way of life, non-white ethnicity, concealing clothing, and insufficient sun exposure are all risk factors, as are pathological illnesses like malabsorption and liver and renal disease. [45]

Fetal Skeletal Mineralization

From 8 to 12 weeks of gestation, the skeleton begins to develop, and the production of synovial joints, chondrogenesis, and osteogenesis must all occur simultaneously. Eighty percent of bone mineral is accreted during third trimester, when, is when bone templates created during intramembranous and endochondral ossification are primarily mineralized. A fetus has higher plasma Ca2+ concentration compared to the mother due to maternal Ca2+ being actively transferred through the placenta during pregnancy.[46]

The convenience of Ca2+ to meet fetal demands is facilitated by a doubling of the fractional absorption of calcium through the mother's intestine beginning as early as 12 weeks' pregnancy and sustained up until birth, and also by resorption of the maternal skeleton throughout the third trimester but in a lesser extent. [46] This is accomplished by changing the levels of certain

maternal calcitropic hormones, such as 1,25(OH)2D and parathyroid-related peptide. [47]

The average fetal skeleton will have about 30 gram of calcium, along with 20 gram of phosphorus, and 0.8 gram of magnesium. During the last six weeks of pregnancy, calcium transfers through the placenta at a rate of 300 mg/day.11 Therefore, it is expected that the limited availability of substrates for bone mineralization, such as those caused by maternal nutrition, compromised intestinal function, maternal vitamin D deficiency, or decreased the function/transfer of placenta, will have a negative effect on bone mineralization through intra uterine life. [48]

Vitamin D During Pregnancy

It is not unexpected that antenatal vitamin D level has been investigated as a potential strategy to enhance the mineralization of skeletal tissue of kids given the significance of maternal vitamin D to the elevation of intestinal calcium absorption.

Pregnant women frequently have biochemically low amounts of 25(OH)D, similar to other population groups.

Since the early 1980s, vitamin D intake during pregnancy has been researched. Despite the large number of clinical trials that have been carried out, we are still unsure about the effects of vitamin D during pregnancy and the ideal dose and time of supplementation. Although its endocrine involvement in calcium homeostasis should not be understated, the significance of vitamin D during pregnancy centers on its immunological activities. [49] The ability of vitamin D to significantly enhance birth outcomes would be at the very top of this list. This assertion is primarily supported by research done in our lab. [50–54] The unmatched, unexplained variations in vitamin D metabolism that occur during pregnancy are a factor that is greatly overlooked. First, as soon as placental implantation takes place, enormous levels of 1,25(OH)2D start to be generated and released into the maternal circulation. [50] During pregnancy, 1,25(OH)2D circulation levels are super physiologic and can occasionally reach 300 pg/mL. [50] In a non-pregnant person, this level of 1,25(OH)2D in the blood would cause hypercalcemia that might be lethal. In our own experience, levels as low as 80 pg/mL can result in hypercalcemia caused by excessively circulating 1,25(OH)2D in situations other than pregnancy.

Where is all of this extra 1,25(OH)2D created during pregnancy? Maternal kidney, fetal kidney, or placenta are the three options. Although 1,25(OH)2D can be produced by all three organs, it is doubtful to come from the fetal kidneys or placenta, particularly at early period of conception. This is because the fetal kidneys do not yet created, and the placenta is very small, with only layers of cells growing out from the blastocyst to connect with the uterus' expanding lining beginning around week 4 to 5. Additionally, a previous in vivo study suggests that maternal kidney production. [55]

Lifestyle, diet, supplement use and geographic latitude influences, and skin pigmentation are significant contributors, even though vitamin D insufficiency affects everyone at all levels. Vitamin D insufficiency is especially dangerous for young children, the elderly, pregnant and nursing women, and people with certain diseases including cancer. [56,57] With variations between nations, maternal vitamin D insufficiency during gestation is another serious global public health issue. For instance, in a research on the white women in the southern UK, 31% had serum 25(OH)D levels below 50 nmol/L and 18% had levels below 25 nmol/L in late pregnancy. In an ethnically more varied area of London, 36% of pregnant women had 25(OH) D levels below 25 nmol/L.[58]

It is reported that 81% of pregnant women in Nepal were deficient during pregnancy [59] , and in more than 90% in Saudi Arabia [60] , and Guizhou, China [61] . A multiple study in Africa reported a prevalence of about 44% in pregnant mothers and newborns. [62] Some countries recommend vit D supplement to pregnant woman's recommended nutritional intake. For instance, 200 International Units (IU)/day of vitamin D is the recommended dietary intake for pregnant women in the America , Canada, Australia and New Zealand [63,64] The UK recommends 400 IU/day during pregnancy [65] When it comes to vitamin D insufficiency, children under the age of five are among the population groups that are most affected. Based on a cutoff value of vitamin D supplementation on birth outcomes, a systematic review and meta-analysis encompassing nations in Africa estimated the prevalence of hypovitaminosis D at 49% and 25% in newborns and children, respectively.

Children aged 0 to 14 in Mosul City have a high frequency of vitamin D deficiency and insufficiency. Only 53.1% of the study participants had enough vitamin D, while the remaining participants either have inadequate vitamin D (21.9%) or deficient vitamin D (25%) levels. Children's vitamin D deficiency is reportedly on the rise. It might be caused by insufficient exposure to the sun, skin pigmentation, skin covering, air pollution, and a decrease intake of vitamin D.

According to this study, vitamin D supplements should be given to all children and adolescents in addition to babies. [66]

Effects of Vitamin D Status on the Fetus, Newborn, Infant and Children

Daily neonatal supplementation with 400 IU of vitamin D quickly develops vitamin D stores in the case of limited maternal-fetal vitamin D transfer, and this will lessen the effects of fetal exposures [67]

When it comes to vitamin D insufficiency, children under the age of five are among the population groups that are most affected. Infants' vitamin D level during the first 6 to 8 weeks of life is mostly reliant on placental transmission in pregnancy. [68] Stores of vitamin D during infancy are depleted by approximately 2 months of age. [69] After then, nutrition, sunlight, and supplementation all contribute to the infant's vitamin D intake. For sustaining appropriate vitamin D levels, human milk is insufficient, especially if sunlight exposure is restricted. [70] Infants who are exclusively breastfed get hypovitaminosis D because of the poor quality of human milk. [71,72] Six weeks to six months postpartum are a crucial window for treating vitamin D insufficiency in infants who are exclusively breastfed. [73] There are several original investigations on the relationship between maternal vitamin D and a child's linear growth, however there is a lack of comprehensive scientific data. In this review, we investigate the relationship between maternal vitamin D level and linear growth in young infants. The results of this synthesis will aid in educating the scientific community on the top areas that need to be researched in order to supplement vitamin D in children's growth. [74]

Evidence for Supplementation and Recommendations

The American College of Obstetricians and Gynecologists also stated in 2011 that a daily dose of 1,000–2,000 IU of vitamin D would be safe in pregnant women with low levels of vitamin D. While 600 IU of vitamin D supplementation is the recommended daily intake for adults. [75] These amounts, according to a recent study by Hollis et al., may be overly conservative and ineffective to provide adequate vitamin D levels during pregnancy. They emphasized that endogenous vitamin D concentrations produced daily from sun exposure, especially in pregnant women, such as 10,000–20,000 IU of vitamin D/day, are significantly lower than the recommended upper safe intake limit, which is 4,000 IU/day for the Institute of Medicine and 10,000 IU/day for the Endocrine Society. [76] Recent research by these authors included two randomized controls studies comparing groups of pregnant women receiving various vitamin D dosages (NICHD trial: 400 IU/day; Thrasher Research Trial: 2,000 IU/day and 4,000 IU/day). [77, 78]. A combined analysis of the two RCTs indicates that supplementing pregnant women with 4,000 IU/day of vitamin D is safe, permits obtaining adequate amounts of vitamin D for both the mother and the fetus, and appears to lower the risk of preeclampsia and infections. [79] There is no any information about the safety of large levels of vitamin D during the first trimester of pregnancy because supplementation didn't begin until the 12th week of pregnancy. Roth et al. discovered that a weekly dose of 35,000 IU might increase maternal vitamin D levels safely and recommended that this regimen of supplement be taken into consideration in future trials. [80]

Last but not least, Dawodu et al. demonstrated that the most efficient dose to increase vitamin D levels during pregnancy with low levels of vitamin D and their offspring is 4,000 IU/day. [81]

Apart from divergent views on dosage, it is generally recognized that vitamin D supplementation during pregnancy is important, especially in light of the common insufficiency in the general population. Before they serve as the foundation for clinical practice, the recent discoveries about the body health advantages for mothers and children should be reviewed. First off, the majority of research on vitamin D during pregnancy is still observational, and there have only been a few RCTs performed thus far. Observational studies should be viewed as articles that generate hypotheses and establish the groundwork for further experiments to confirm earlier findings. [82] Two recent meta-analysis reach the same conclusion [83,84] , claiming that because there are not enough high-quality trials, there is now only weak evidence that vitamin D supplementation during pregnancy would be beneficial for mother or child.

Notably, however, the aforementioned most recent RCTs have not yet been included in a meta-analysis. Finally, while vitamin D supplements should be given to all pregnant women, special consideration should be assumed to those who are at a great risk of hypovitaminosis D. Specifically due to limitations of vitamin D metabolism by seasonal or pathological disorders,consent should be achieved on customized supplementation for women having the risk factors of limited or incompetent sun exposure. [85,86]

RECOMMENDATIONS

The organization restates that the cutoff values of 12 ng/mL, 12–20 ng/mL, and >20 ng/mL for serum 25-hydroxy vitamin D are considered for vitamin D deficiency, insufficiency, and sufficiency, respectively. Serum 25OHD >100 ng/mL with hypercalcemia and/or hypercalciuria is the definition of vitamin D toxicity. During infancy, 400 IU/day of vitamin D supplementation is advised; however, older children and adolescents should get their recommended daily allowance of 400–600 IU/day of vitamin D from their diets and from natural sources, such as sunlight. Oral cholecalciferol should be used to treat rickets and vitamin D deficiency, preferably on a daily dosage plan of 2000 IU for 12 weeks. [87]

CONCLUSION

The correct mineralization of bones during childhood depends on vitamin D. Although enough amounts of this mineral should be provided by diet and sun exposure, vitamin D deficiency rickets are extremely common worldwide. The greatest risk of developing nutritional rickets in children is associated with certain diseases that result in reduced vitamin D production and/or absorption. Severe forms of vitamin D resistant or dependent rickets are also linked to a number of uncommon genetic abnormalities.

Maternal vitamin D levels during pregnancy may have an impression on the duration of pregnancy as well as the health of the fetus and kid. The appropriateness of supplements and advised doses during pregnancy is a contentious topic.

A fascinating and exciting area of study deals with the effects of vitamin D supplementation on pregnant women and how effective it is. However, as the results of the present studies are still inconclusive, more research is required to help clinicians navigate the dense body of literature. In the near future, it is hoped that a supplement this straightforward and seemingly efficient would enhance pregnancy outcomes and both maternal and child health.

REFERENCES

1. Tan ML, Abrams SA, Osborn DA. Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD013046. DOI: 10.1002/14651858.CD013046.pub2.
2. Hollis, B.W.; Wagner, C.L. Substantial Vitamin D Supplementation Is Required during the Prenatal Period to Improve Birth Outcomes. Nutrients 2022, 14, 899. https://doi.org/10.3390/nu14040899
3. Pludowski, P.; Takacs, I.; Boyanov, M.; Belaya, Z.; Diaconu, C.C.; Mokhort, T.; Zherdova, N.; Rasa, I.; Payer, J.; Pilz, S. Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement. Nutrients 2022, 14, 1483. https://doi.org/10.3390/nu14071483
4. Hollis BW, Roos BA, Draper HH, P W Lambert. Vitamin D and its metabolites in human and bovine milk. J Nutr. 1981;111:1240–1248 . DOI: 10.1093/jn/111.7.1240.
5. Sizar O, Khare S, Goyal A, Amy Givler. Vitamin D Deficiency. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 cited 2022 Feb 24]. Available from 2022 Feb 24. http://www. ncbi.nlm.nih.gov/books/NBK532266/
6. Holick MF. Vitamin D Deficiency. N Engl J Med. 2007;357:266–281. doi: 10.1056/NEJMra070553.
7. Khazai N, Judd SE, Tangpricha V. Calcium and vitamin D: skeletal and extraskeletal health. Curr Rheumatol Rep. 2008;10:110–117. doi: 10.1007/s11926-008-0020-y.
8. Bikle DDVDM. Mechanism of action, and clinical applications. Chem Biol. 2014;21:319–329. doi: 10.1016/j.chembiol.2013.12.016.
9. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev. 2016;96:365–408.DOI: 10.1152/physrev.00014.2015
10. Fernández-Cancio M, Andaluz P, Torán N,Esteban C,Granada M. Vitamin D stimulates growth hormone-insulin-like growth factor (GH-IGF) gene axis expression and potentiates gh effect to reverse the inhibition produced by glucocorticoids in human growth plate chondrocytes. HRP. 2007;67:204–205. doi: 10.1016/j.ghir.2008.10.004.
11. Ameri P, Giusti A, Boschetti M, Marta Bovio, Claudia Teti, Giovanna Leoncini, et al. Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency. Eur J Endocrinol. 2013;169:767–772. doi: 10.1530/EJE-13-0510.

12. Institute of Medicine (US). Committee to review dietary reference intakes for vitamin D and calcium. In: Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary reference intakes for calcium and vitamin D. Washington (DC): National Academies Press (US). 2011 cited 2022 Jun 16. Available from: http://www.ncbi.nlm.nih.gov/books/NBK56070/
13. Giustina A, Adler RA, Binkley N, Bollerslev J,Bouillon R,Dawson-Hughes B, et al. Consensus statement from 2nd international conference on controversies in Vitamin D. Rev Endocr Metab Disord. 2020;21:89–116. doi: 10.1007/s11154-019-09532-w.
14. Cashman KD. 100 YEARS OF VITAMIN D: global differences in vitamin D status and dietary intake: a review of the data. Endocr Connect. 2022;11:cited 2022 Mar 16:Available from https://ec.bioscientifica.com/view/journals/ec/11/1/EC-21-0282.xml. doi: 10.1530/EC-21-0282
15. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S,Köstenberger M,Tmava A ,et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74:1498–1513. doi: 10.1038/s41430-020-0558-y.
16. Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa M, Brown K, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018;1430:44–79. doi: 10.1111/nyas.13968
17. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. Nat Rev Dis Primers (2017) 3:1–20. doi: 10.1038/nrdp.2017.101
18. Dahash BA, Sankararaman S. Rickets.," StatPearls (2022). Treasure Island (FL: StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/books/ NBK562285/ (Accessed August 19, 2022).
19. Wharton B, Bishop N. Rickets. Lancet (2003) 362:1389–400. doi: 10.1016/ S0140-6736(03)14636-3
20. Sabbagh Y, Carpenter TO, Demay MB. Hypophosphatemia leads to rickets by impairing caspase-mediated apoptosis of hypertrophic chondrocytes. Proc Natl Acad Sci U.S.A. (2005) 102:9637–42. doi: 10.1073/pnas.0502249102
21. Goltzman D. Functions of vitamin d in bone. Histochem Cell Biol (2018) 149:305–12. doi: 10.1007/s00418-018-1648-y
22. Thacher TD, Pludowski P, Shaw NJ, Mughal MZ, Munns CF, Högler W. Nutritional rickets in immigrant and refugee children. Public Health Rev (2016) 37:3. doi: 10.1186/s40985-016-0018-3
23. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab (2016) 101:394–415. doi: 10.1210/jc.2015-2175
24. Sahay M, Sahay R. Renal rickets-practical approach. Indian J Endocrinol Metab (2013) 17:S35–44. doi: 10.4103/2230-8210.119503
25. Rauch F. The rachitic bone. Endocr Dev (2003) 6:69–79. doi: 10.1159/000072770
26. Julies P, Lynn RM, Pall K, Leoni M, Calder A, Mughal Z, et al. Nutritional rickets under 16 years: UK surveillance results. Arch Dis Child (2020) 105:587–92. doi: 10.1136/archdischild-2019-317934
27. Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin d–deficiency rickets among children in Canada. CMAJ (2007) 177:161–6. doi: 10.1503/cmaj.061377
28. Chabra T, Tahbildar P, Sharma A, Boruah S, Mahajan R, Raje A. Prevalence of skeletal deformity due to nutritional rickets in children between 1 and 18 years in tea garden community. J Clin Orthop Trauma (2016) 7:86–9. doi: 10.1016/ j.jcot.2016.01.005
29. Jones HL, Jammeh L, Owens S, Fulford AJ, Moore SE, Pettifor JM, et al. Prevalence of rickets-like bone deformities in rural Gambian children. Bone (2015) 77:1–5. doi: 10.1016/j.bone.2015.04.011
30. World Health Organisation. Nutritional rickets: a review of disease burden, causes, diagnosis, prevention and treatment. 1st ed (2019). Geneva. Available at: https://www.who.int/publications-detail-redirect/9789241516587 (Accessed December 6, 2022).
31. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr. 2008;88(2):491S-499S. doi: 10.1093/ajcn/88.2.491S.
32. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3): 266-81. doi: 10.1056/NEJMra070553.
33. Battault S, Whiting SJ, Peltier SL, Sadrin S, Gerber G, Maixent JM. Vitamin D metabolism, functions and needs: from science to health claims. Eur J Nutr. 2012;52(2):429-41.]
34. Barrett H, McElduff A. Vitamin D and pregnancy: An old problem revisited. Best Pract Res Clin Endocrinol Metab. 2010;24(4): 527-39.
35. Hossein-nezhad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. PLoS One. 2013;8(3):e58725.

36. Wagner CL, Taylor SN, Dawodu A, Johnson DD, Hollis BW. Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus. Nutrients. 2012;4(3):208-30.
37. Kovacs CS. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. Am J Clin Nutr. 2008;88(2):520S-528S.
38. Lapillonne A. Vitamin D deficiency during pregnancy may impair maternal and fetal outcomes. Med Hypotheses. 2010;74(1): 71-5.
39. Thandrayen K, Pettifor JM. Maternal vitamin D status: implications for the development of infantile nutritional rickets. Endocrinol Metab Clin North Am. 2010;39(2):303-20.
40. Snellman G, Melhus H, Gedeborg R, Byberg L, Berglund L, Wernroth L, Michaëlsson K. Determining vitamin D status: a comparison between commercially available assays. PLoS One. 2010;5(7):e11555.
41. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53-8.
42. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.
43. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol. 2010;202(5):429.e1-9.
44. Bischoff-Ferrari HA. Vitamin D: role in pregnancy and early childhood. Ann Nutr Metab. 2011;59(1):17-21.
45. Fanos M, Vierucci F, Saggese G. Vitamin D in the perinatal period: an update. J Pediatr Neonat Individual Med. 2013;2(2):e020202. doi: 10.7363/020202
46. Rebecca J. Moon , Elizabeth M. Curtis, Stephen J. et al. The importance of maternal pregnancy vitamin D for offspring bone health: learnings from the MAVIDOS trial, Ther Adv Musculoskel Dis 2021, Vol. 13: 1–14).
47. More C, Bhattoa HP, Bettembuk P, Balogh A. The effects of pregnancy and lactation on hormonal status and biochemical markers of bone turnover. Eur J Obstet Gynecol Reprod Biol 2003; 106: 209–213. doi: 10.1016/s0301-2115(02)00237-3.
48. Kovacs CS. Maternal mineral and bone metabolism during pregnancy, lactation, and post-weaning recovery. Physiol Rev 2016; 96: 449–547.
49. TheodoratouE, Tzoulaki I, ZgagaL , Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomized trials. British Journal of Nutrition. 2017. 118: 550–558.
50. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M., et al. Vitamin D inthe healthy eurepianpaediatric population: a position paper by the ESPGHAN Committee on Nutrition. J PediatrGastroenterolNutr. 2013. 56: 692–701. DOI: 10.1097/MPG.0b013e31828f3c05
51. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J., et al.Vitamin D and calcium: asystematic review of health outcomes. Evid Rep Technol Assess (Full Rep). 2009.183:1–420.
52. Katrinaki M, Kampa M, Margioris A, Castanas E, Malliaraki N. Vitamin D levels in a large Mediterranean cohort:reconsidering normal cut-off values.HORMONES. 2016. 15(2):205-223.
53. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, HeaneyRP.,et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J ClinEndocrinolMetab.2011. 96: 1911-1930.DOI: 10.1210/jc.2011-0385
54. Rosen CJ. Clinical practice. Vitamin D insufficiency . N Engl J Med 2011;364:248-54.DOI: 10.1056/NEJMcp1009570
55. Miettinen ME, Kinnunen L, Leiviskä J, Keinänen-Kiukaanniemi S, Korpi-Hyövälti E, Niskanen L, et al.Association of Serum 25-Hydroxyvitamin D with Lifestyle Factors and Metabolic and Cardiovascular Disease Markers: Population-Based Cross-Sectional Study (FIN-D2D). PLoS ONE 2014,9(7): e100235. doi:10.1371/journal.pone. 0100235.
56. Casey CF, Slawson DC, NealLR.Vitamin D Supplementation in Infants, Children, and Adolescents. 2010. 81(6): 745- 748. www.aafp.org/afp.
57. Gupta MM., Round JM., and StampTCB.Spontaneous cure of vitamin-D deficiency in Asians during summer in Britain. The Lancet.1974.303(7858):586-588. https://doi.org/10.1016/S0140-6736(74)92648-8.
58. McAree T, Jacobs B, Manickavasagar T, Sivalokanathan S, Brennan L, Bassett P ,et al. Vitamin D deficiency in pregnancy – still a public health issue. Matern Child Nutr 2013; 9: 23–30. doi: 10.1111/mcn.12014.
59. McLaughlin, M., Raggatt, P.R., Fairney, A., Brown, A., Brown, D.J., Lester, E. & Wills, M.R. Seasonal variations in serum 25-

hydroxycholecalciferol in healthy people.The Lancet. 1974. 303(7857):536-538. https://doi.org/10.1016/S0140-6736(74)92717-2
60. Lund B and Sorensen OH. Measurement of 25-hydroxyvitamin D in serum and its relation to sunshine, age and vitamin D intake in the Danish population.Scand. J. clin. Lab. Invest. 1979.39:23- 30.DOI: 10.3109/00365517909104935 .
61. Poskitt E, Cole TJ , Lawson DEM . Diet, sunlight, and 25-hydroxy vitamin D in healthy children and adults. British Medical Journal. 1979. 1:221-223.
62. Osborn TW. The 25-hydroxycholecalciferol chick serum binding protein system: isolation, characterizationand utilization to develop a specific competitive-binding radioassay for 25-hydroxycholecalciferol,a metabolite of vitamin D3. Dissert. Abstr.B. 1976. 37: 2694. doi: 10.1210/jcem-33-6-992.
63. Cheng Q, Du Y, Hong W, Tang W, Li1 H, Chen M and Zheng S.Factors associated to serum 25-hydroxyvitamin D levels among older adult populations in urban and suburban communities in Shanghai, China. BMC Geriatrics. 2017. 17:246. DOI 10.1186/s12877-017-0632-z
64. Casey CF, Slawson DC and Neal LR. Vitamin D Supplementation in Infants, Children, and Adolescents. 2010. 81(6): 745- 748. www.aafp.org/afp.
65. Bikle DD. Vitamin D: Newer Concepts of Its Metabolism and Function at the Basic and Clinical Level. Journal of the Endocrine Society. 2020. 4(2):9-10.https://doi.org/10.1210/jendso/bvz038.
66. Fawzi et al (2021): Vitamin D prevalence in Nineveh Province © Annals of Tropical Medicine & Public Health DOI: http://doi.org/10.36295/ASRO.2021.24528
67. Razaghi M, Olusola F, Sotunde F, Olusola F , Shu Qin Wei, McNally D, et al. Maternal excess adiposity and serum 25-hydroxyvitamin D BMC Pregnancy and Childbirth (2022) 22:83 https://doi.org/10.1186/s12884-022-04403-w
68. Hillman LS, Haddad JG. Human perinatal vitamin D metabolism I: 25-Hydroxyvitamin D in maternal and cord blood. J Pediatr. 1974;84:742–749. doi: 10.1016/s0022-3476(74)80024-7.
69. Ala-Houhala M. 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. J Pediatr Gastroenterol Nutr. 1985;4:220–226. doi: 10.1097/00005176-198504000-00011.
70. Hollis BW, Roos BA, Draper HH, et al. Vitamin D and its metabolites in human and bovine milk. J Nutr. 1981;111:1240–1248. doi: 10.1093/jn/111.7.1240.
71. Dawodu A, Agarwal M, Hossain M, et al. Hypovitaminosis D and vitamin D deficiency in exclusively breast-feeding infants and their mothers in summer: a justification for vitamin D supplementation of breast-feeding infants. J Pediatr. 2003;142:169–173. doi: 10.1067/mpd.2003.63.
72. Balasubramanian S, Ganesh R. Vitamin D deficiency in exclusively breast-fed infants. Indian J Med Res. 2008;127:250–255.
73. Tareke AA, Hadgu AA, Ayana AM, Zerfu TA. Prenatal vitamin D supplementation and child respiratory health: a systematic review and meta-analysis of randomized controlled trials. World Allergy Organ J. 2020;13:100486. doi: 10.1016/j.waojou.2020.100486.
74. Amare Abera Tareke, Addis Alem, Wondwosen Debebe, Nebiyou Simegnew Bayileyegn, Melese Shenkut Abebe, Hussen Abdu & Taddese Alemu Zerfu (2022) Maternal vitamin D and growth of under-five children: a systematic review and meta-analysis of observational and interventional studies, Global Health Action, 15:1, DOI: 10.1080/16549716.2022.2102712
75. Khan SR, Whiteman D, Kimlim MG, Janda M, Clarke MW, Lucas RM, Neale RE. Effect of solar ultraviolet radiation exposure on serum 25(OH)D concentration: a pilot randomised controlled trial. Photochem Photobiol Sci. 2018;17: 570-7. doi: 10.1039/c7pp00378a.
76. Datta P, Philipsen PA, Olsen P, Petersen B, Andersen JD, Morling N, et al. Pigment genes not skin pigmentation affect UV-B-induced vitamin D. Photochem Photobiol Sci. 2019;18:448–58. doi: 10.1039/c8pp00320c.
77. Sachdeva S. Fitzpatrick skin typing: Applications in dermatology. Indian J Dermatol Venereol Leprol. 2009;75:93-6. doi: 10.4103/0378-6323.45238.
78. Cashman KD, Sheehy T, O'Neill CM. Is vitamin D deficiency a public health concern for low middle - income countries? A systematic literature reviews. Eur J Nutr.2019; 1-21. GUPTA ET AL. REVISED IAP VITAMIN D GUIDELINES INDIAN PEDIATRICS 25 DECEMBER 29, 2021 [E-PUB AHEAD OF PRINT]
79. Millen AE, Bodnar LM. Vitamin D assessment in population-based studies: A review of the. Am J Clin Nut. 2008;87:1102S–1105S. doi: 10.1093/ajcn/87.4.1102S.
80. Mac Laughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest. 1985;76:1536-8. doi: 10.1172/JCI112134.
81. Harinarayan CV, Holick MF, Prasad UV, Vani PS, Himabindu G. Vitamin D status and sun

exposure in India. Dermato endocrinol. 2013;5:130–41. doi: 10.4161/derm.23873.
82. Hettiaratchy S, Papini R. Initial management of a major burn: II--assessment and resuscitation. BMJ. 2004;329:101-103. doi: 10.1136/bmj.329.7457.101.
83. Specker BL, Ho ML, Oestreich A, Edwards N, Tsang RC. Sunshine exposure and serum 25-hydroxyvitamin D concentrations in exclusively breast-fed infants. J Pediatr. 1985;107:372-6. doi: 10.1016/s0022-3476(85)80509-6.
84. Rockell JE, Green TJ, Murray C, Susan J. Season and ethnicity are determinants of serum of serum 25(OH)D concentration in New Zealand children aged 5-14 yr. J Nutr. 2005; 135: 2602-8. doi: 10.1093/jn/135.11.2602.
85. Rajakumar K, Holick MF, Jeong K, Charity G , Tai C , Olabopo F, et al. Impact of season and diet on vitamin D status of African American and Caucasian children. Clin Pediatr (Phila). 2011;50:493–502.doi: 10.1038/s41564-019-0376-y
86. Raizada N, Goyal A, Singla R, Sreenivas V, Gupta N, Khadgawat R. Changing trend in vitamin D status from 2008 to 2016: An experience from a tertiary care institute in North India. Indian J Endocrinol Metab. 2020; 24: 150-4. doi: 10.4103/ijem.IJEM_634_19.
87. Larry A. Greenbaum Vitamin D Deficiency (Rickets) and Excess. In Robert M. Kliegman, Richard E. Berman, Nelson Textbook of Pediatrics,21 ed .Elsevir 2020; p:2003-2004.