IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Vitamin D: A Brief Review

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Abstract: *Vitamin D* refers to a group of fat-soluble secosteroids It is essential for maintaining healthy bones and teeth. It also plays many other important roles in the body, including regulating inflammation and immune function. The present review highlights the sources of Vitamin D, vitamin D synthesis, its function, reasons for Vitamin D deficiency and measures to overcome its deficiency and Vitamin D status in pregnant women and Neonates.

Key Words: Secosteroids, inflammation, immune function

Introduction:

Vitamin D refers to a group of fat-soluble secosteroids (is a type of steroid with a "broken" ring) responsible for increasing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. The most important compounds in this group in case of humans are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (Ergocalciferol) **(***Holick MF; 2006). Vitamin D_3 (Cholecalciferol) is produced from the conversion of 7-dehydrocholesterol in skin and vitamin D_2 is produced by some plant life in response to UV radiation, example in mushrooms.*

Vitamin D is an important nutritional factor in the health of the mother and her infant. Vitamin D regulates expression of >1000 genes in humans, and vitamin D receptors are found in several tissues/cells in the human body **(GindeAA *et al;* 2010).**

The classical and non-classical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection, and cancer **(Garland CF *et al*; 2006).** Vitamin D deficiency can cause skeletal as well as extra skeletal diseases. Vitamin D is involved in bone formation, resorption, and mineralization and in maintaining neuromuscular function.

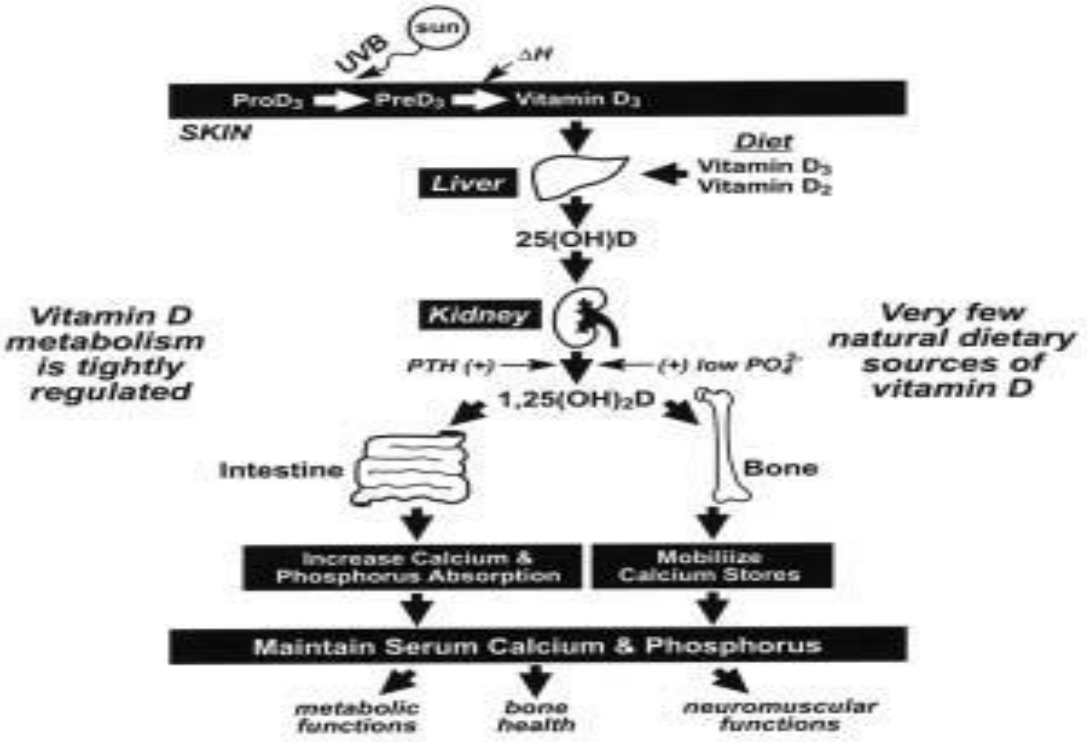
It is important for multiple physiologic processes. In recent years there has been an increased understanding of the role that vitamin D plays in regulation of cell growth, immunity, and cell metabolism

Sources of *Vitamin D*

Plasma 25(OH) D or calcidiol (a summation of D_2 and D_3 forms) is the most reliable marker of Vitamin D status. Vitamin D_3 is produced in the skin on exposure to sunlight. Vitamin D_3 is derived from 7-dehydrocholesterol by ultraviolet irradiation of the skin. The most important source of vitamin D is the skin's synthesis of the Vitamin from UV B solar radiation **(Holick MF; 2004)**. Any process that reduces UV B photons from entering the epidermis will diminish cholecalciferol (Vitamin D_3) production. Sunlight is less effective in producing Vitamin D_3 in persons with darker skin because the ultraviolet light is absorbed by the skin pigment **(Clemens TL *et al*; 1982, Harris SS and Dawson-Hughes B; 1998).** The skin pigment melanin absorbs UV B photons and can reduce vitamin D_3 synthesis by >90% **(Clemens TL *et al*; 1982).**

Dietary sources of Vitamin D are limited. Vitamin D_3 is found in animal food sources e.g., fatty fish (like salmon, mackerel and tuna), cod liver oil, milk, etc. Vitamin D_2 is found in vegetal sources like sun-exposed yeast, mushrooms and plant sterol; ergosterol. Notably, most dietary sources are not sufficiently rich in their Vitamin D content.

Vitamin D Photobiochemistry and Metabolism



UV-B irradiation in skin triggers photolysis of 7-dehydrocholesterol (provitamin D_3) to previtamin D_3 in the plasma membrane of human skin keratinocytes (**Holick MF; 1994, MacLaughlin JA *et al;* 1982, Holick MF *et al;*1995).** Once formed in the skin, cell plasma membrane previtamin D_3 is rapidly converted to Vitamin D_3 by

the skin's temperature. Vitamin D_3 from the skin and Vitamin D from the diet undergo 2 sequential hydroxylations, first in the liver to 25(OH)D and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Excessive solar UV-B irradiation will not cause Vitamin D intoxication because excess Vitamin D_3 and previtamin D_3 are photolyzed to biologically inactive photoproducts **(MacLaughlin JA *et al;* 1982, Holick MF *et al;* 1995, Webb AR *et al*; 1989).** Melanin, skin pigmentation is an effective natural sunscreen, and increased skin pigment can greatly reduce UV-B mediated cutaneous synthesis of Vitamin D_3 by as much as 99%, similar to applying a sunscreen with a sun protection factor of 15 **(Clemens TL *et al*; 1982, Matsuoka LY *et al*; 1987).** Keratinocytes are also capable of hydroxylating 25(OH)D to produce $1,25(OH)_2D$**.** The $1,25(OH)_2D$ (from keratinocyte or renal sources) may regulate keratinocyte differentiation, melanocyte apoptosis, and melanin production **(Bikle DD; 2005),** and this may be another mechanism for regulating the cutaneous synthesis of Vitamin D_3 by negative feedback.

$1,25(OH)_2D$ is released in blood, where it binds to Vitamin D binding protein (DBP) and reaches its target tissues to exert its endocrine functions through the Vitamin D receptor (VDR). $1,25(OH)_2D$ is also produced in several extra renal tissues for its paracrine and autocrine functions. Most cells in the body have VDR.

Skin synthesis of Vitamin D usually contributes 80% to 90% Vitamin D supply in free-living persons. This assumption is based on the fact that in healthy young adults circulating 25(OH)D concentrations usually lie between 30-80 nmol/L **(McKenna M.J; 1992)**, dietary Vitamin D intake is usually below 5 µg daily **(Zittermann A; 2003)**, and 1 µg Vitamin D increases circulating 25(OH)D concentrations by approximately 1-3 nmol/L **(Vieth R; 2009, Patel M *et al*; 2008)**. The exact amount of Vitamin D production in human skin depends on the geographic latitude, season, time of day, as well as on the weather conditions (cloudiness), amount of air pollution and surface reflection. In addition, clothing habits, lifestyle, and workplace (e.g., indoor versus outdoor), sunscreen use, and sun avoidance practices have a strong impact on Vitamin D synthesis.

Functions of *Vitamin D*

Vitamin D and Skeletal Health

Rickets, osteomalacia and osteoporosis are widely prevalent all over the world. The most well recognized function of Vitamin D involves regulation of calcium and phosphorus balance for bone mineralization and remodeling. Without adequate levels of Vitamin D in the bloodstream, dietary calcium cannot be absorbed. Low calcium levels lead to an increase in serum Parathyroid Hormone (PTH) concentration, which leads to increased tubular reclamation of calcium in kidneys and resorption from the skeleton at the cost of lowering bone density. In the long term this leads to weakened and brittle bones that break easily. Approximately 40%–60% of total skeletal mass at maturity is accumulated during childhood and adolescence. Rickets results from inadequate mineralization of growing bone. Thus it is a childhood disease and it is manifested as bone deformities, bone pain and weakness. Biochemical abnormalities consistently include hypophosphatemia, elevated alkaline phophatase levels and serum 25(OH)D levels are usually below 5 ng/mL. Chronic Vitamin D deficiency in adults results in osteomalacia, osteoporosis, muscle weakness and increased risk of falls **(Ritu G. and Ajay Gupta; 2014).**

Vitamin D: Extra skeletal Effects

- **Vitamin D and Muscle Strengthening**

Vitamin D deficiency causes reduced aktomyosin content of myofibrils, low calcium content of mitochondria, reduced calcium uptake into the sarcoplasmic reticulum, and low serum levels of muscle enzymes **(Zittermann A.; 2003).** The importance of Vitamin D-repletion for adequate muscle function was underscored in a recent study in institutionalized people ≥60 years of age with insufficient Vitamin D status **(Moreira-Pfrimer L.D.; 2009)**

- **Immunity**

There is mounting evidence for a pivotal role of Vitamin D in the immune system. Calcitriol is able to induce the differentiation of monocytes into macrophages. In addition, calcitriol increases the activity of macrophages and facilitates their cytotoxic activity. Macrophages represent the first unspecific defense line of the immune system. It is well known that the prevalence of infections such as pneumonia is high in infants with rickets **(Zittermann A.; 2003).** The use of Vitamin D (or cod liver oil) as a treatment of infections have been practiced for over 150 years. As early as 1903, Niels Finsen was awarded the Nobel Prize for Medicine and Physiology for his theory to cure Lupus vulgaris (skin-tuberculosis) using phototherapy. In **2007, Schauber *et al;*** published data demonstrating that Vitamin D is able to stimulate synthesis of the anti-microbial peptide cathelicidin in human skin cells to enhance innate immunity.

- **Cancer**

Since Vitamin D is a key regulator of various cellular metabolic pathways, it is important for cellular maturation, differentiation, and apoptosis **(Zittermann A.; 2003)**. In 2008, the WHO published a report from the International Agency for Research on cancer that came to the conclusion that there is (i) consistent epidemiological evidence for an inverse association between 25(OH)D and colorectal cancer and colorectal adenomas, (ii) suggested epidemiological evidence for an inverse association between 25(OH)D and breast cancer, (iii) insufficient evidence for an inverse association between 25(OH)D and other types of cancer, and (iv) the need for new randomized controlled trials (RCTs) **(WHO; 2008)**.

- **Type 1 Diabetes**

Type 1 diabetes is caused by autoimmune destruction of pancreatic β cells, which eventually leads to insulin-dependent diabetes. Higher rates of incidence of type 1 diabetes were observed at higher latitudes worldwide **(Karvonen M *et al*; 2000, Mohr S.B *et al*; 2008).** Epidemiological association of Vitamin D intake and reduced risk of type 1 diabetes was also seen **(Hypponen *et al*; 2001)**. A meta-analysis of observational studies showed a 30% reduction in risk of type 1 diabetes in children receiving Vitamin D supplements **(Zipitis, C.S. *et al;* 2008).**

- **Type 2 Diabetes**

Type 2 diabetes is marked by insulin resistance (IR). In insulin resistance insulin is adequately or overproduced by pancreatic β cells, but is ineffectively utilized by the target cells of adipose, hepatic and skeletal muscles tissues. As a response to hyperglycemia, β cells further increase insulin production leading to hyperinsulinemia, which is often indicative of a pre-Type 2 diabetes stage. Hyperinsulinemia is associated with hypertension, obesity, dyslipidemia, and glucose intolerance **(Modan M. *et al*; 1985)**. These conditions are collectively known as "metabolic syndrome". A meta-analysis of observational studies showed inverse relation of Vitamin D levels and calcium status with insulin resistance and hyperglycemia. In this meta-analysis, supplementation with both the nutrients combined showed benefit in optimizing glucose levels **(Pittas, A.G. *et al*; 2007).**

- **Cardiovascular Health**

Cardiovascular diseases (CVDs), including heart failure and coronary artery disease are a major cause of morbidity and mortality worldwide. There is accumulating epidemiological evidence from observational studies suggesting that Cardiovascular diseases are associated with Vitamin D deficiency **(Wang T.J *et al*; 2008, Ginde A.A *et al*; 2009).** Increased risk of hypertension was associated with living at higher latitudes **(Rostand S.Gl; 1997).** Vitamin D level < 21 ng/mL was associated with increased risk of hypertension, diabetes, obesity and high triglyceride levels- all associated with increased cardiovascular mortality **(Martins D. *et al*; 2007).** Various studies have reported reduced Vitamin D concentrations in patients with previous and prevalent cardiovascular or cerebrovascular diseases **(Brewer L.C. *et al*; 2011, Pilz S. *et al*; 2011).**

Vitamin D Sufficiency via Sun Exposure Is Not a Tenable Solution for Most Indians

Vitamin D deficiency is a major health concern in India, notwithstanding the brightly shining sun. The "adequacy of exposure to sunlight of an individual's bare skin" required to photosynthesize Vitamin D is grossly ill understood. Darker skin has high melanin content which acts as a natural sunscreen. Therefore, darker skin produces a significantly lesser amount of Vitamin D when compared with the individuals with fairer skin **(Lo C.W. *et al*; 1986, Clemens T.L. *et al*; 1982, Matsuoka L.Y. *et al*; 1991)**.

Thus, for Indian skin tone, minimum "direct sun exposure" required daily is more than 45 min to bare face, arms and legs to sun's UV rays (wavelength 290–310 nm). With the exception of those who perforce need to work outdoors in the sun, most Indians do not get adequate sun exposure to produce sufficient amounts of Vitamin D endogenously. Indian social and or religious norms related to public modesty dictate that most parts of an individual's body, irrespective of gender, be covered. The not so D-lightful price of urbanization -in big cities a majority of people live in very high population density areas. They perforce live in overcrowded tenements, which are closely packed and 3-4 stories high. Consequently, direct sunlight does not reach inside.

Nutritional Factors Attributing to High Prevalence of Vitamin D Deficiency in India

Most dietary sources of Vitamin D have very low Vitamin D content. Most of the food items rich in Vitamin D are of animal origin. Most Indians are vegetarians. Commonly, a dietary source of Vitamin D for vegetarians is milk, provided milk has been fortified with Vitamin D. Milk is rarely fortified with Vitamin D in India. The Vitamin D content of unfortified milk is very low (2 IU/100 ml). Additionally, milk and milk products are unaffordable to the socioeconomically underprivileged. Another concern in India is the rampant dilution and/or adulteration of milk and milk products.

Low Calcium in Indian diet: Low dietary intake of calcium in conjunction with Vitamin D insufficiency is associated with secondary hyperparathyroidism (SHPT). SHPT is further exacerbated by induced destruction of 25(OH)D and $1,25(OH)_2D$ by 24 hydroxylase **(Jones G. et al; 2012)**. 24 hydroxylase is the key enzyme of Vitamin D catabolism and is regulated by $1,25(OH)_2D$, PTH and FGF23 (Fibroblast Growth Factor 23) levels. FGF23 is a phosphate regulator. High serum phosphate levels increase production of FGF23 in bone osteocytes via the action of $1,25(OH)_2D$. Subsequently, FGF23 reduces renal phosphate resorption, indirectly suppresses intestinal phosphate absorption and also suppresses PTH and $1,25(OH)_2D$ synthesis. Overproduction of FGF23 can result in increased morbidity associated with Vitamin D deficiency **(Liao E; 2013)**. This regulatory mechanism may explain the low 25(OH)D levels in rural subjects on a high phytate and/or low calcium diet, despite plentiful sun exposure.

Intake of caffeine from tea and coffee is very high in India. Most Indians consume milk as part of their tea or coffee. The proportion of milk is very low in these drinks. Thus calcium intake through these beverages is low. Vitamin D is stable during cooking. It is stable up to 200 °C. However, thermal stability of Vitamin D is an inverse function of both temperature and time.

In India, milk is boiled for several minutes before consumption. Before the same lot of milk is consumed in entirety, it is subjected to two-three rounds of boiling. In India most of the times, beverages like tea and coffee are boiled for several minutes to get the right flavor. This boiling may reduce the content of any Vitamin D that there may have been left after boiling of the milk itself. Therefore, these beverages may not contribute significantly to either calcium or Vitamin D intake in Indians.

Indian diet has high phytate content. Phytate is the principle storage form of phosphorus in many plant tissues, especially the bran portion of grains and other seeds. Phytate is indigestible to humans. Phytates chelate micronutrients such as calcium and iron, and thus reduce intestinal absorption of these nutrients.

Need for Vitamin D Fortified Food Products in India

Vitamin D sufficiency via sun exposure is untenable for most Indians, as discussed earlier. Vitamin D rich dietary sources are unaffordable and mostly limited, especially for vegetarians. Most Indians are vegetarians. Vitamin D supplements are unaffordable and not feasible as a population based approach. Fortification of widely

consumed staple foods with Vitamin D is the only viable solution towards attaining Vitamin D deficiency in India. Unlike supplementation strategies, fortification of food with Vitamin D poses a negligible risk of toxicity.

Food Items Which Could Be Fortified with Vitamin D in India

- Milk: The whole array of different grades of milk available could be fortified-whole milk, toned, double toned and skim milk.
- Milk curd and yogurt.
- Infant formulas.
- Butter, ghee (clarified butter) and oils, to use as spreads or to spike already cooked food.
- Soy milk, soy curd (tofu), orange juice and mango juice may be fortified to cater to the needs of the lactose intolerant individuals and those who are allergic to milk proteins. Processed cheese also has very low lactose content and is rich in calcium and may be fortified for the benefit of the lactose intolerant. Due to high prevalence of dyslipidemia, metabolic syndrome and cardiovascular diseases in India, these fortified items will also offer healthier choices to the general population.
- Widely consumed and affordable staple food items such as chapati flour, maida (all purpose wheat flour, used to make bread and other bakery products), rice and rice flour may be suitable vehicles for fortification strategies in the Indian scenario.

Foods Fortified with Vitamin D Available in the Indian Market

Vitamin D fortified milk from Amul® (an Indian dairy cooperative, located in Anand, Gujarat,India) is the only fortified milk product found in the general market. It has 4.5% fat, homogenized milk fortified with calcium 150 mg, Vitamin A 75 μg and Vitamin D 0.5 μg (20 IU), etc., per 100 mL. The expiry date of this milk is 120 days if the carton is unopened. Incidentally, with a 10% or more loss per month at 4 °C, there is not much Vitamin D left by 120 days. It may be hoped that storage temperatures are always adhered to. But in India this is a remote possibility due to economical and technical limitations. In a brief survey, most retailers reported that the Amul® milk cartons supplied to them were generally one month past expiry date already at the time of delivery and that the demand for this product was very low.

Vitamin D deficiency is pandemic, yet it is the most under-diagnosed and under-treated nutritional deficiency in the world **(Mithal *et al*; 2009).** Vitamin D deficiency is widespread in individuals irrespective of their age, gender, race and geography. Vitamin D is photosynthesized in the skin on exposure to Ultra Violet B (UV-B) rays. Sun exposure alone ought to suffice for vitamin D sufficiency. Vitamin D deficiency is prevalent in India, a finding that is unexpected in a tropical country with abundant sunshine. There are few data from India about the prevalence of hypovitaminosis D in pregnancy and in the newborn (**Sachan A *et al*; 2005).**

Cultural and social taboos often dictate lifestyle patterns such as clothing- that may limit sun exposure and vegetarianism- which certainly limits vitamin D rich dietary options. Most Indians are vegetarians. The

socioeconomically backward people constitute a large percentage of the population in India. The underprivileged generally suffer from overall poor nutrition.

Increasing urbanization that precludes outdoor exposure to the sun and elevating levels of air pollution can cause a low status of vitamin D **(Chailurkit LO *et al;* 2011).** Air pollution containing ozone absorbs UV-B photons and results in a reduction of cutaneous photosynthesis of precholecalciferol (**Holick MF; 1994).**

In a population that already has a high prevalence of Vitamin D deficiency and poor dietary calcium intake, the problem is likely to worsen during pregnancy because of the active transplacental transport of calcium to the developing fetus.

Vitamin D deficiency in pregnant women may affect the women as well as their unborn children. The deficiency could lead to a high bone turnover, bone loss, osteomalacia, and hypovitaminosis D myopathy in the mother (**Glerup H *et al;* 2000, Lips P*;* 2001).**

A newborn's vitamin D stores are completely reliant on vitamin D from the mother (**Hollis BW and Pittard WB III; 1984).** Most studies of vitamin D deficiency during pregnancy have shown negative effects on calcium homeostasis and skeletal mineralization of the (unborn) child, eg, the occurrence of congenital rickets, craniotabes, and lower bone mineral content (**Hollis BW and Pittard WB III; 1984, Specker BL; 1994, Arden NK *et al;* 2002, Namgung R & Tsang RC; 2003).** Rickets during infancy has been associated with higher prevalence of lower respiratory tract infections **(Muhe L *et al*; 1997)**, the largest cause of infant mortality in India.

Role of Vitamin D in Pregnant Women

Adequate Vitamin D intake is essential for maternal and fetal health during pregnancy, and prevention of adverse outcomes. Recent work emphasizes the importance of non-classical roles of Vitamin D in pregnancy and the placenta. Vitamin D deficiency during pregnancy is associated with the non-classical actions of this Vitamin, being linked with preeclampsia, insulin resistance, gestational diabetes mellitus**(MacKay AP, *et al*; 2001),** bacterial vaginosis, and an increased risk for caesarean section delivery. Women who have Vitamin D deficiency do not usually feel any different but in some may have muscle weakness and weakened bones.

A study finds that women who develop severe preeclampsia tend to have lower blood levels of Vitamin D than healthy pregnant women raising the possibility that the Vitamin D plays a role in the complication. Preeclampsia rates are elevated during winter months, when sunlight-dependent Vitamin D productions are reduced. Vitamin D supplementation reduces preeclampsia risk, compared to un supplemented controls **(Marya RK; 1987)**.

Vitamin D is known to influence insulin secretion. $1,25(OH)_2D$ regulates insulin secretion by pancreatic β-cells and thereby affects circulating glucose levels**(Chiu KC *et al*; 2004).** Vitamin D deficiency during early pregnancy significantly increases the risk for gestational diabetes in later pregnancy **(Bell NH *et al*; 1985).**

Reclamation Vitamin D may influence the course of infectious diseases during pregnancy. Low Vitamin D levels are correlated with increased bacterial vaginosis in the first trimester.

Role of Vitamin D in Newborn and Infant

Fetal Vitamin D concentrations are mainly dependent on maternal concentration, and maternal deficiency may lead to adverse outcomes in offspring. Vitamin D-deficiency in mothers have significantly increased risk of infantile rickets due to inadequate maternal–fetal transfer of 25-hydroxyvitamin D **(Russell JG and Hill LF.; 1974).** Recent retrospective studies found a significant and previously undetected association of maternal Vitamin D deficiency with rickets-associated infant heart failure and with acute lower respiratory tract infection **(Salle BL *et al*; 1998),** a serious complication often associated with sepsis without clinical signs of rickets.

A few studies have observed that maternal Vitamin D concentrations are related to offspring birth weight and growth during the postnatal years. Lower maternal Vitamin D status was associated with lower bone mineral concentration and impaired glucose homeostasis in newborn infants. Maternal Vitamin D deficiency also has been associated with craniotabes, a softening of skull bones that is one of the earliest signs of Vitamin D deficiency **(Scholl TO and Chen X.; 2009)**, in a case study with neonatal seizures of a hypocalcemic infant and with impaired skeletal development in utero. Interestingly, Vitamin D deficiency during pregnancy is also associated with risks of health problems later in childhood, including improper bone development at 9 yrs of age, asthma **(Reif S *et al*; 1988),** dental cavities, schizophrenia, and type I diabetes **(Mannion CA *et al*; 2006, Weiss ST and Litonjua AA; 2008, Wagner CL and Greer FR; 2008).**

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