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Research Article

WHAT HAS CHANGED IN THE LAST 5 YEARS; VITAMIN D DEFICIENCYIN PREGNANCY

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ABSTRACT

To evaluate the present status of vitamin D deficiency in pregnant patients in a one year time period all pregnant patients consecutively assesed for their serum vitamin D levels. Values according to seasons grouped. A very high vitamin D deficieny was observed .Vitamin D levels were below 20 ng/ml in 90 percent of the pregnant patients. Results were compared with a previous research that was done five years ago and no significant improvement was observed.

Objectives: to determine the present prevalence of vitamin D deficiency in pregnant women and compare with former prevalence rates.

INTRODUCTION

Vitamin D deficieny (VDD) is regarded as a worldwide health problem almost in epidemic proportions. You can see reports about its prevalence in almost all countries in the world. Formerly considered as an active ingredient in Ca^{++} and bone metabolism now its activities and receptors are uncovered in inflammation regulation, immunity, immune responses, intestinal permeabilty, insulin activity and sugar metabolism .In pregnancy, association studies point a possible relation between vitamin D (VD)and adverse outcomes of pregnancy such as abortion, growth retardation, preeclampsia gestational diabetes and maybe difficulty in the delivery of babies with increased cesarean section rates. Many studies measured VD levels in late pregnancy; researchers assesed VD levels in early pregnancy to intervene.

MATERIAL AND METHOD

In 2016, 623 pregnant women in their first trimester in an inner city district of Istanbul with a population of 300,000 people were evaluated consecutively for their VD serum values, under pregnancy surveillance at a district hospital in Istanbul. Throughout the world to assess VD status serum assays for 25 (OH) VD are used. Because the half life of 25(OH) VD is 2-3 weeks and this value reflects both skin production and dietary intake. This is currently the best marker for VD status. Serum vitamin D values were assesed by HPCLA method in this research.

RESULTS AND DISCUSSION

Vitamin D (VD) is a fat soluble vitamin that is found in fatty fish, liver, egg yolk and mushroom in significant concentrations; almost nonexistent in plants. (2,3) (Holick 2007; Holick 2008). Human skin can produce this vitamin from 7 dehydrocholesterol under ultraviolet B (UVB) radiation.. In fact majority is formed endogenously within the skin.(4,5) (Hollis2013) (DeLuca 2004). Two physiologically active forms exist; one of them is called vitamin D2 also known as ergocalciferol. The other form is vitamin D3; cholecalciferole which is found in animal sources and formed by the break of a bond in 7 dehydrocholesterol molecule with ultraviolet B irradiation in sun rays. This form is also present in aforementioned VD containing foods. From the solar radiation that enters the atmosphere, Ultraviolet (UV) radiation has wavelengths 200-400 nm, further divided into UVA (315–400 nm) UVB (280–315 nm) and UVC(200-280 nm) Ozone and other molecules, block UVC (200–280 nm), which does not reach the surface.(6,7) (Godar DE, Juzeniene A) It has been suggested that the skin area exposed should be large to reduce the duration of exposure. Exposing a larger skin area more often is safer, as a long exposure on a limited area could lead to sunburn in fair-skinned people and would not result in additional vitamin D synthesis.(8) Webb VD supplementations in foods are in the form of VD3 and this form is three times more active than VD2. As a drug VD3 is three times more active compared to VD2 in raising serum concentrations. This

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form is more readily bound to VD carrying proteins in blood.(9,10,11) (Armas 2004; Logan 2013;McCullough 2007).Because the half life of VD is short to maintain sufficient levels it must be taken in sufficient quantities continuously.

Metabolism of VD2 and VD3 are thorough the same activating and degrading enzymatic pathways. First it undergoes 25 hydroxylation in the liver than transforms into 1, 25 dihydroxy D3 in the kidney by 1 alpha hydroxylase enzyme. 1, 25 $(OH)^2$ D3 is the metabolically active form in the body. It activates nuclear VD receptors in target tissues and organs. Renal conversion in kidney proximal tubules into active form is under the contol of parathormone(PTH). Receptors sensing the plasma Ca levels are located in parathyroid glands (PTG). When Ca levels fall parathormone is secreted from PTG. There is a unique interaction between VD and calcium levels.PTH increases serum calcium levels thorough osteoclastic bone resorbtion but 1,25 VD3 increases calcium from extraskeletal sources by increasing intestinal absorbtion and renal reabsorbtion.

For some researchers Vitamin D resembles a prohormone which is active in the skin, intestines, bone, parathyroid gland ,brain and pancreas. It has been shown to be active in the development of intestines and colon in fetal life. (12) (Theodoropoulos 2003) It has also been reported to regulate insulin secretion in pancreatic beta cells thorough vitamin D nuclear receptors.). (13,14,15,16) (Clifton-Bligh 2008; Maghbooli 2008; Palomer 2008; Xuan 2013) By maintaining calciım homeostasis VD regulates glucose metabolism indirectly.(16)(Xuan 2013)

There is a unique interaction between VD and calcium levels.PTH increases serum calcium levels thorough osteoclastic bone resorbtion but 1, 25 VD3 increases calcium from extraskeletal sources by increasing intestinal absorbtion and renal reabsorbtion.

The Institute of Medecine announced >20 ng/ml VD values as sufficient in 2010.

(17) (Institute of Medicine 2010)This value is valid for both pregnants and general polpulation. For some researchers optimum value should be >32 ng/ml because PTH suppression and Ca absorbtion reaches a plateau at this level. Bone loss, falls and fractures in the elderly are decreased at these levels.(18,19) (Dawson-Hughes 2005;Dawson-Hughes 2008). It is a moot point whether this higher levels proposed for adults are sufficient for pregnants. Production in the skin, intestinal absorbtion and degradation determines the VD status. Melanin content of the skin, clothing habits, seasons, latitude and sunscreen lotions all are factors in this status. (Holick 2007). Precipitation of VD in fatty tissues lowers its bioavailability in obese individuals.(20) (Drincic 2012. This is simple dilution of VD in fat. 21(Arunabh 2003). Fat dilution lowers VD levels in obese and high BMI individuals.(22,23,24) (Vilarrasa 2007; Vimaleswaran 2013;Wortsman 2000Sedantery living lowers VD by decreasing sun exposure.S edantery living limiting exposure to sun rays accompanies low VD levels.

Vitamin D has a crucial role during pregnancy, as it is necessary for optimal fetal growth. Insufficiency has been associated with a spectrum of adverse outcomes for the embryo, neonate, infant, growing child and mother. These outcomes include pre-eclampsia, preterm birth, fetal growth restriction, stillbirths, gestational diabetes and hypertension. (25) Nassar N In the literature there are reports showing the associations between low VD and unwanted complications of pregnancy. It is observed that preeclampsia risk in pregnancy is increased %78 in VD deficient pregnants. (26) (Aghajafari 2013).Also in preeclamptic pregnancies low VD levels were observed. This may be related to implicitor explicit biological mechanism relevant to immune dysfunction, implantation of placenta, abnormal angiogenesis, increased inflammation and hypertension. Thorough these mechanisms VD can affect early development of placenta.(27,28,29,30,31 (Bodnar 2007; Cardus 2006; Evans 2004; Hewison1992; Li 2002) But there are contrasting reports that do not show an association.Yet evidence is inconclusive in this regard.

VD deficiency in early pregnancy is associated with later development of gestational diabetes mellitus. (32,33) (GDM) (Farrant2009; Zhang 2008) A meta analysis show %49 increaed risk for GDM.

Although exact mechanism unclear sufficient VD level seems protective against other unwanted complications of pregnancy. For instance some authers detected an association between cesarean birth and VD deficiency.(34,35) (Merewood 2009;Scholl 2012)but the mechanism is not resolved; it is argued that VD deficiecy could cause pelvic musculature weakness but it is not proven. On the other hand it is an established fact that VD deficiecy causes high bone turnover bone loss, osteomacia and muscular weakness.(36,37,38)(El Koumi 2013; Glerup 2000; Lips 2001).

There may be also an inverse association between preterm birth and VD levels.(39,40) (Dawodu 2011; Merley 2006). A meta analysis evaluating two observational study supports the association between small for gestational fetus and low VD values.(41)(Wei 2013) A recent study showed VD deficiency in 97 percent of mothers whose children were rachitic.(42) (Dawodu 2005)

Recently autocrine activity of VD has been disclosed with identification of 1 alpha hydroxylase activity and vitamin D receptors in multiple organs, tissues and cells. VD has autocrine influences on both adaptive and innate immune system.(43,44) (Miller 2010;walker 2009)because macrophages and monocytes have both 1 alpha hydroxylse activity and VDR.

According to Mc Gath prenatal and perinatal VD deficiecy can increase multiple sclerosis, cancer, insulin dependent diabetes mellitus and schizophrenia risk in future years.(45)Mc Gath 2001 Children whose mothers were vitamin D insufficient during pregnancy may be at a greater risk for brain tumors, multiple sclerosis, type 1 diabetes, schizophrenia, allergic rhinitis and asthma. (46)

In children VD deficiency is related with TYPE 1 diabetes mellitus, Multiple sclerosis, allergies, and atopic diseases.(47,48,49) (Bener 2009; Miller 2010; PİERROT Deseilligyn 2010)

Despite reports favoring the association between maternal vitamin D deficiency and childhood asthma some reports found no relation between asthma and VDD in children.(50)Meral G

Multiple studies support a strong association between VDD and tuberculosis, pneumonia, cystic fibrosis. (51,52,53,54) (Chocano 2009; Hall 2010; nnoaham 2008; Williams 2008)

Fetal programming of diseases in adulthood due to inadequate and/or excess of macronutrients and energy was originally proposed by Barker. (55)(Barker DJ) There are a studies indicating the role of VD in the formation and growth of lungs.(56,57) (Deveraox 2007, Litonjuan 2009)

Vitamin A and D receptors are expressed throughout the brain thereby potentially affecting many of the brain regulatory functions by acting as molecular switches that activate genes through their respective receptors.(58,59) Abnormal brain development and links between neuropsychiatris disorders and VDD has been proposed by some authors.(59)

Studies of vitamin D deficient (VDD) rodent models have consistently shown that vitamin D is required for brain development whereby the brains of offspring from VDD mothers are characterized by a mild brain shape distortion, increased lateral ventricle volumes, reduced differentiation and diminished expression of neurotrophic factors. Vitamin D receptors (VDRs) are widely expressed at various gestational stages of the rat embryonic brain, such as in the spinal cord, medulla oblongata, pons, midbrain, diencephalon, cortex, basal ganglia, cerebellum and choroid plexus. The expression of VDRs in the developing brain of the rat peaks during gestational days 15-23.(60,61)

In contrast to other fat soluble vitamins, vitamin D has been extensively reviewed in the context of developmental deficiency and neurological diseases, i.e., schizophrenia, autism, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis (62) DeLuca

Children whose mothers were vitamin D insufficient during pregnancy may be at a greater risk for brain tumors, multiple sclerosis, type 1 diabetes, schizophrenia, allergic rhinitis and asthma. (63)

VD plays a major role in human reproduction and VD deficiency and insufficiency have been associated with a variety of adversemater-nal and fetal outcomes, such as increased risks of gestational diabetes, RPL, preeclampsia and fetal growth restriction (41)

Previously, It was reported that 45% of RPL patients had VD deficiency and women with VD deficiency had an increased prevalence of auto antibodies including APA, anti thyroperoxidase antibody, antibodies to anti- nuclear antigens and anti-ssDNA antibody when compared with those of RPL patient with normal VD levels.

VD deficiency is common among APS patients and it is often associated with clinically defined thrombotic events in APS patients. VD inhibits anti-β2-GPI-mediated tissue factor (TF) expression. Hence, VD deficiency induces increased TF expressions, which result in sequential thrombosis in APS. Thrombotic events at maternal fetal junction may lead to RPL in patients with APS. Women with RPL and VD deficiency had 2.68 times higher risk to have anti-thyroperoxidase antibody than those with RPL and normal VD level [9]. VD deficiency is linked with high levels of thyroid auto antibodies, abnormal thyroid function, increased thyroid volume and TSH levels [35], and VD was shown to prevent autoimmune thyroiditis by inhibiting lymphocyte proliferation and secretion of inflammatory cytokines. VD deficiency is also associated with the prevalence of ANA, and in SLE patient VD supplementation significantly decreased ANA titers.(64,65)

Currently VD deficiency is an established public health issue worlwide but its prevalence in pregnants is not searched for all countries in the world. In some countries there are researches presenting whole country but in others there are individual limited low scale studies for its prevalence. It is highly prevalent even in sunny countries.(66,67,68) (Bandeira 2006; Palacios 2014; van Schoor 2011) Prevalence is high even in sunny countries. The highest prevalences are in girls and wemen in the countries in the middle east.

There are 17 prevalence studies in pregnant and lactating women; two studies from American continent, six from Europe, one from Africa, seven from Oceania.

Distribution of below 20 ng/ml VD levels in some countries are as follows in pregnant and lactating women. Data from other countries are lacking or scarce.

Vitamin D Deficiency in Pregnant Patients in Some Countries	
USA	% 33
Canada	% 24
Belgium	% 45
England	% 44
Holland	% 44
Spain	% 20
Germany	% 77
Tanzania	% 1
Turkey	% 90
Iran	% 67
Pakistan	% 45
Kuwait	% 38-45
India	% 60
Australia	% 48

(67)(Palacios 2014)

The prevalence of vitamin D insufficiency during pregnancy varies worldwide from 18 to 84%. (68)In China, 22.4% of pregnant women were deficient during summer and 65.8% during winter. (69) Jiang L Dressing style seems to be a risk factor for hypovitaminosis D during pregnancy. This phenomenon was evident in studies from Muslim Mediterranean countries (70 Halicioglu O, 71 Haliloglu B,72 ParildarH,73Ustuner I 74 Pehlivan I)

A study in turkey on pevalence of VD in pregnant women was done in 2012 in the last trimester of pregnancy. In that study prevalence was on the order of 90 percent.(70) (Halicioglu O.)In this study we observed very high rates on the order of 90 percent in pregnant women in a similar fashion in the first trimester of pregnancy. (Table 1) A research on prevalence of VDD in children, adolescents adults in the same research district found an important difference in the values of vitamin D between genders favouring males. VD deficiency was 33.4 percent and insufficiency was 40.4 percent in females for all age groups, but through adolescence prevalences rose. This finding were atributed to routine VD supplementation directed to preschool age children through public health authorities' intervention. (75) Meral G. (Ethno Medecine 2016)

Table 1 Distribution of vitamin D values in all pregnant women between 15-43 years old (Total 632 pregnant women)

Vitamin D value	Number of pregnant women	%
0 - 5 ng/ml	163	25,8
5 -10 ng/ml	263	41,6
10 -15 ng/ml	98	15,5
15 - 20 ng/ml	52	8,2
>20 ng/ml	56	8,9

Seasonal variations are seen in VD values. Prevalence is significantly higher in winter in comparison to summer and autumn. Latitude is also effective in this regard. (2) (Hollick 2008)

Table 2 shows range distribution of vitamin D values in pregnant women in different seasons. Seasonal vitamin D deficiency distributions are shown in tables 3,4,5,6. VDD reaches a summit in winter and decreases progressively until late summer. When VD values of pregnant patients in winter season were compared to fall VD values there is a statistically significant difference (p 0.5) Vitamin D values rose progressively through summer and reached a peak in fall self evidently

Table 2 Seasonal ranges of vitamin D values

Seasonal range	N	The ranges of vitamin D distribution
fall	167	3-35,4
winter	245	2.3- 40,6
spring	164	2.6- 50,8
summer	56	1.5-65.3

Health organizations recommendations for VD varies between 200 IU/day and 400IU/day for maintenance. But many researchers advocate optimum VD levels 30 ng/ML or higher. To attain this levels they recommend 1000-1600 IU/day VD intake.(76)(Dawson-Hughes 2005)

Table 3

Vitamin D values in spring		%
0 - 10 ng/ml	109	66,5
10 - 20 ng/ml	42	25,6
>20 ng/ml	13	7,9
Total n	164 pregnant	

The requirement in pregnancy for both therapy and maintenance is not clear. Some researchers propose 1000 IU daily intake to reach levels above 20 ng/ml. (77) (HOLLİS 2004)

Table 4

Vitamin D values in summer		%
10-10 ng/ml	25	44,6
10 - 20 ng/ml	18	32,1
>20 ng/ml	13	23,2
Total n	56 pregnant	

The Endocrine Society suggests that pregnant and lactating women require at least 600 IU/d of vitamin D and recognize that at least 1500–2000 IU/d may be needed tomaintain sufficient blood concentrations of 25(OH)D.(78)Holick

Table 5

Vitamin D values in fall		%
0 -10 ng/ml	108	64,7
10- 20 ng/ml	40	24,0
>20 ng/ml	19	11,4
Total n	167 pregnant	

On the other hand daily clinical practice does not incorporate holistic approach and guidelines foroptimal sun exposure for pregnant women.(79) Beltran AJ

Table 6

Vitamin D values in winter		%
0 - 10 ng/ml	182	74,3
10 - 20 ng/ml	51	20,8
>20 ng/ml	12	4,9
Total n	245 pregnant	

CONCLUSIONS AND RECOMMENDATIONS

VDD seems highly prevalent at the present time so health authorities should search and take the necessary steps to prevent the still high VDD in pregnancy when compared with former years.

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