 DOI: 10.18231/2394-2754.2017.0074

Insight into Vitamin D Deficiency: an obstretical outlook

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Received: 10th May, 2017 **Accepted:** 4th October, 2017

Introduction

Vitamin D deficiency has been linked with various adverse health outcomes as a result of which it attracts the attention in research field in current days. In this way, Vitamin D deficiency has influenced upon adverse pregnancy outcomes. Over the last decade studies have been done with systematic reviews and meta analysis in epidemiologic literature.[1,2] Likewise, it is gaining importance over its classical action in health in recent era as it has some non-classical actions such as immunomodulation, anti-inflammatory, insulin secretion enhancement etc.[3]

Vitamin D, pleotropic secosteroid hormone has two forms:

1. Vitamin D_3 or chloecalciferol
2. Vitamin D_2 or Ergocholecalciferol

Cholecalciferol is produced from 7-Dehydrochloecalciferol in skin and the second one ergocalciferol is the produced in the mushrooms and yeast.[4] In the liver vitamin D is changed to calcidiol and calcidiol is converted to calcitriol in kidney by various enzymatic reactions.[4] Calcidiol being the major circulating form represents most appropriate nutritional status. On the other hand, calcitriol is the active form of vitamin D.

Sunlight is main source of vitamin D in adults.[5] It is said that half an hour of sunlight deliver 50000 IU of vitamin D in white skin whereas dietary supply make a small contribution as little vitamin D occurs naturally in food.[5] Thus from the factors that inhibit its synthesis in skin, poor dietary intake and additional factors affecting its absorption and metabolism ultimately results in vitamin D deficiency.[6]

No expert opinion till date exists regarding its optimum level to maintain overall health. It is agreed that a serum level of at least 20 mg/ml is required to avoid bone problems.[7] But "Institute of Medicine" has defined vitamin D deficiency as a level less than 50 nmol/litre and insufficiency between 50-75 nmol/litre.[8] An expert opinion is still in need regarding optimum level of vitamin D during pregnancy.

Physiological changes of vitamin D metabolites during pregnancy

During pregnancy to acquire extra calcium for adequate foetal bone mineralisation significant changes occur in vitamin D.[9] Actually, the foetus may accumulate up to 30 gm of calcium at term and to stratify this demand, vitamin D metabolism is boosted in order to increase calcium absorption.[10] These changes include in maternal serum level of:

1. Renal and placental CYP27B1(vitamin D activating enzyme)
2. Placental vitamin receptor (VDR)
3. Calcitriol
4. Vitamin D binding protein (DBP)

During pregnancy time, surprisingly changes in calcidiol and calcium level are not seen.[11] Even after the increase of calcitriol, maternal calcium does not increase. It may be due to foetal transfer of calcium and concomitant normal rise in maternal calciuria precluding risk of hypercalcemia.[12]

Effects in Pregnancy: Calcidiol is the best indicator of vitamin D in serum and it remains constant throughout the pregnancy time.[11] So there may be increment in serum calcitriol level which is independent of changes in its precursor synthesis.[13] Calcidiol crosses placenta which represents main pull of vitamin D in foetus.[13] Therefore, vitamin D deficient mother can give birth to a vitamin D deficient baby.[14]

From first trimester of pregnancy, calcitriol doubles its concentration up to end of third trimester and return back to normal value after delivery.[15] It is to be noted that this physiological rise is related to increase synthesis rather than clearance.[16] This increase concentration of calcitriol is due to increase in the level of an enzyme which is related to vitamin D anabolic reaction i.e.CYP27B1.This enzyme is found in maternal kidney, placental trophoblast and deciduas.[17] Upregulation of placental transport and absorption of calcium is mainly attributed to calcitriol and this increased calcium absorption can be linked to adequate fetal bone mineralisation near term.[18]

Calcitrol has a dual role in immunomodulation.[19] It aims to improve innate immune response and on the other hand restrains exaggeration of inflammation during inplantation.[19] The underlying mechanism is inhibition of expression of pro inflammatory cytokines (TNF α, interferon γ and IL-6) and simultaneous induction of potent endogenous antimicrobial peptides (hCTD, B defensins HBD-2, HBD-3) and antagonisation of IL-10, a physiological suppressor of maternal active immunity.[19,20]

Hormoneogenesis form placenta is immensely influenced by calcitriol. It also plays a great role in overall placental physiology like endometrial desidualisation, synthesis of estradiol and progesterone. It also regulate two most important hormone in pregnancy i.e. Placental lactogen expression and Human chorionic gonadotropin.[21]

From the above points, it is presumed that vitamin D deficiency during pregnancy may contribute to variety of pregnancy associated disorders i.e. preeclampsia, gestational diabetes mellitus, bacterial vaginosis, premature rupture of membranes (PROM), preterm birth, increase rate of primary caesarean section, recurrent abortion etc.[22]

Preeclampsia is the specific disorder of pregnancy. It occurs all over the world up to 3-5% of total pregnancies. It has been linked with increasing incidence of maternal, fetal and neonatal morbidity and mortality.[23] Although there is a better progress towards understanding the pathophysiology, still no effective therapy has been discovered to prevent early termination of pregnancy associated with preeclampsia.[23] According to JM Roberts hypothesis, it develops in two stages. He states that decreased placental perfusion is usually secondary to abnormal trophoblastic invasion with consequent failed dilatory remodelling of maternal vessels perfusing placenta that precedes and results in clinical manifestations of these disorder.[24] Multiple factors are linked with development of preeclampsia. They are endothelial dysfunction, syncytiotrophoblast micro particles and inflammatory reaction, antiangiogenic factors, maternal constitutional factors etc.[25] On going to discover the mechanism causing preeclampsia, experts gave opinion that vitamin D deficiency may be associated with an increased risk of preeclampsia.[23] Extensive studies have been done regarding this association. Bodnar and co-workers also studied this matter and came to a conclusion that maternal vitamin D is a clear risk factor for developing preeclampsia.[26] In the same way a Norwegian study also revealed 25% decrease in risk of preeclampsia in the population who had increased dietary intake of vitamin D.[27]

Four other independent metanalyses found a statistically significant association between preeclampsia and low maternal vitamin D levels.[28,29,30,31] Robinson and colleague showed 63% decrease in preeclampsia risk where increment in the serum vitamin D level of study population seen.[32] From these studies, it may be said that maintaining vitamin D sufficiency is a simple measure to prevent preeclampsia which is a major cause of maternal mortality and morbidity. However, some other study groups were of opposite opinion. According to them no association exists between low serum vitamin D level and development of preeclampsia.[33,34]

GDM is prevailing worldwide, reaching almost 15-20%.[35] Those women who are not getting effective treatment to manage gestational diabetes will have to face increasing risk of developing type II DM after pregnancy. Their off springs are also at increased risk of developing childhood obesity and type II DM later on.[36] Since 1980, a constantly growing body of evidence is supporting the connection between vitamin D and insulin or glucose metabolism.[37] Everybody is not of the same opinion regarding the mechanism governing Calcitriol and glucose metabolism connection. It is suggested by one group of experts that Calcitriol can regulate intracellular calcium influx on ß pancreatic cells and thus help in modulating insulin release.[38] Some experts are of opinion that calcitriol is responsible for various cellular reactions of glucose metabolism. These are upregulation of muscle insulin receptor substrate 1(IRS-1), adipocyte GLUT4 protein and its translocation to the cell surface. Normal activity of Glucose metabolic enzymes such as fructose 1, 6 bisphosphatase; hexokinase; glucose 6 phosphatase also regulated by calcitriol.[39] It is hypothesised that placentas from GDM mothers have higher expression of CYP24A1(vitamin D catabolising enzyme) which results into low serum calcitriol level and this results in altered glucose metabolism.[40] In spite of consistently growing studies linking vitamin D deficiency in GDM, data investigating this relationship is still inconsistent. Poel and co-workers also made metanalysis and suggested significant association between vitamin D deficiency and GDM.[41] Sante et al concluded from their studies that maternal vitamin D deficiency is associated with markers of altered glucose homeostasis.[42] However, in some other studies contradictory findings are also seen which showed no significant association between the two.[43,44]

Bacterial vaginosis is commonly seen in women of all reproductive age groups. During pregnancy, it gains a lot of attraction as it can complicate pregnancy by causing PROM and preterm delivery.[45] Data found on national health and nutritional examination (NHANES) 2001-14 has revealed that vitamin D insufficiency or deficiency had a statistically significant association with bacterial vaginosis only among pregnant women.[46]

Moreover, it can also prevent other kind of infections during pregnancy. Some scientists found that vitamin D supplementation can induce a gene called hCTD which prevent uropthogenic E coli and other bacterial infections.[47]

It is known that oxytocin and conexin 43 are two proteins, which cause uterine contraction. According to experts, calcitriol alone or along with lipopolysaccharide endotoxin decreases expression of these two proteins in myometrial smooth muscle cell of uterus. In this way, calcitrol can modulate uterine quiescence even under bacterial infection and can prevent abnormal uterine contractions that favour PROM and preterm delivery.[48]

In present time, it is presumed that due to vitamin D deficiency rate of primary caesarean section is increasing. Anne et al opined that rate of primary caesarean section increase by four fold in vitamin D deficient women compared to those who are not. Explanation for their findings is that skeletal muscle contains vitamin D receptors. Proximal muscle weakness and reduced strength due to vitamin D deficiency cause poor muscle performance.[49,50] Thus poor pelvic musculature make vaginal delivery difficult by decreasing the mother's ability to push.

One of common pregnancy complications is foetal growth restriction. It affects up to 5% of pregnancy all over the world.[51] Recent studies highlight the importance of supplementation of vitamin D by which we can prevent fetal growth restriction.[52] Murthi P et al demonstrated decreased vitamin D receptors in placentas of growth restricted foetus which may be a cause of abnormal apoptosis of trophoblast and abnormal regulation of gene related to cell cycle growth in vitro.[51] So for normal functioning of placenta and fetal growth vitamin D plays an important role.[51]

Some investigators found association between neonatal sepsis and low cord blood vitamin D.[53] Again, Hart et al concluded from their study that maternal vitamin D is a critical factor for the optimal development of fetal organs such as lung, brain and bone as they noticed impaired lung development, neurocognitive disorders, eating disorders in adolescence, bone mass reduction in offsprings of vitamin D deficient mothers.[54]

Hypocalcaemic seizures in neonate and infants may be due to low vitamin D.[55] Increase incidence of wheeze, asthma in offspring is seen in the cases of low maternal vitamin D during pregnancy compared to normal maternal vitamin D.[55]

It is said that recurrent miscarriage is the result of low circulating vitamin D .Wang LQ et al concluded from their study that women with recurrent pregnancy loss have a lower level of CYP27B1 expression in chorionic villi and deciduas compared with normal pregnant women. This reduced CYP27B1 lead to low serum vitamin D ultimately which results in recurrent abortions.[56]

From the above study, it is learned that vitamin D is very important for prevention of several adverse effects, which can potentially threaten the pregnancy outcome. It is, so mandatory to maintain adequate level of vitamin D throughout the pregnancy as it is involved in many biological processes during pregnancy.

Vitamin D: Screening and supplementation (RCOG, ACOG, WHO).

RCOG: There are not any facts and figure to support routine screening for vitamin D deficiency in pregnancy for health benefits or cost effectiveness. Regarding screening test of a pregnant woman somebody may argue on the basis of skin colour or coverage, obesity, risk for preeclampsia or gastroenterological condition limiting fat absorption. Measurement of vitamin D in hypocalcemic or symptomatic women as a part of their management continues to be applicable. This includes women with a low calcium concentration, bone pain, gastrointestinal disease, alcohol abuse, a previous child with rickets and those receiving drugs which reduce vitamin D.[57,58]

ACOG: For recommendation of screening for all pregnant women for vitamin D deficiency still there is lack of consensus in present time. One group of experts are of the opinion that serum vitamin D level of the women who are at risk should be considered and interpreted.[59]

Supplementation: RCOG

Supplementation	**Daily units**	**Combined with**
All pregnant women	400 IU	N/A
High risk for preeclampsia	800 IU	Calcium
High risk for vitamin D deficiency	1000 IU	N/A
Treatment		
Cholecalciferol	2800 IU	20000 IU a week
Ergocalciferol	2800 IU	10000 IU twice weekly

Vitamin D can be safely supplemented in pregnancy. Importance of vitamin D should be told to every pregnant and lactating mother according to UK chief medical officers and NICE guidelines in 2012. They should take 10 micro grams of vitamin D daily.[60] In case of high-risk women prominent care should be taken.

They recommended 3 categories of vitamin D supplementation.

1. Vitamin D 400 IU is (10 µg) a day is recommended for all pregnant women in accord with national guidance.[60]
2. Women at risk (dark colour, reduced exposure to sunlight, obese) should take 1000 IU a day.[61] RCOG has highlighted the importance of addressing suitable advice to these women. Women at risk for preeclampsia are advised to take 800 IU with calcium.[27]
3. Treatment for majority of women who are deficient of vitamin D treat for 4-6 week, either with cholecalciferol 20000 IU or ergo calciferol 10000 IU twice a week, followed by standard supplementation is appropriate.[62] For women who require short term repletion 20000 IU weekly appears to be effective and safe treatment of vitamin D deficiency. A daily dose is likely to be appropriate to maintain subsequent repletion (1000 IU daily). A study group in 2011 demonstrated that supplemental dose 4000 IU cholecalciferol a day

was safe in pregnancy and most effective compared to lower dose.[63]

Although there is insufficient evidence supporting supplementation of vitamin D or treatment, it is not harmful and may have some significant short and long term health benefits even. Of course, research should focus on potential benefits and optimal dosing of vitamin D use in pregnancy.

ACOG

During pregnancy and lactation adequate supplementation of vitamin D should be 600 IU/day according to Food and Nutrition Board at the Institute of Medicine of National Academies.[64] Daily intake should be higher than that recommended by the food and nutrition board to maintain maternal vitamin D sufficiency according to the authors of a recent clinical report from the committee on nutrition of the American academy of paediatrics. Although there is no appropriate data on the safety of higher doses, yet most experts agree that supplemental vitamin D is safe in dosage up to 4000 IU per day during pregnancy or lactation.[64] When vitamin D deficiency is identified during pregnancy, most of the experts agree that 1000 - 2000 IU per day vitamin D is safe. Higher dose regimens used for treatment of vitamin D deficiency during pregnancy are not extensively studied.[59] Still yet, for prevention of preterm birth or preeclampsia, there is no sufficient evidence to recommend vitamin D supplementation during pregnancy.

WHO

For prevention of preeclampsia WHO does not strongly recommend vitamin D supplementation during pregnancy. Moreover, available evidence regarding pros and cons of supplementing vitamin D during pregnancy is limited. On the other hand, it is also not recommended the use of this intervention during pregnancy as a part of routine antenatal care for improving maternal health outcomes. It may be termed as conditional recommendation only.

In cases of proved deficiency, WHO recommends vitamin D supplementation as 200IU/day. Vitamin D may be given alone or as fortified formula for improving maternal serum vitamin D concentration. Pregnant women are advised by WHO to receive adequate nutrition which is best achieved through conjunction of a healthy balanced diet, and to refer to guidelines on healthy eating during pregnancy.

From the above discussion, we have come to know that more interventional and basic studies are required to understand the role of vitamin D during the time of pregnancy. In spite of the fact that vitamin D has a protective role in pregnancy outcomes and it has high prevalence of hypovitaminosis D around the world, still it is suggested that routine vitamin D screening is not mandatory and for this purpose enough interventional studies have not yet been under taken to achieve a consensus for vitamin D supplementation in pregnant women, highlighting the need for further studies and establishment for screening guidelines during pregnancy.

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