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FREQUENCY OF VITAMIN D DEFICIENCY IN PREGNANT WOMEN AT TERTIARY CARE HOSPITAL

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Abstract:

Objective: *To determine the frequency of Vitamin D deficiency in pregnant women visiting a tertiary care facility.*

Material and Methods: *This cross sectional study was conducted in duration of six months from 01-01-2017 to 30-06-2017 at Shaikh Zaid Women Hospital Larkana taking116 patients of age 16-845 years, having alive singleton pregnancy, any gestational age and having proximal muscle weakness bone tenderness were consecutively selected. Patients with chronic renal and cirrhosis, taking medications like anticonvulsant or Glucocorticoids, vitamin D replacement therapy or having a history of osteomalaciawere excluded. Mean ± SD, frequencies & percentages were calculated. Chi-square was used as test of significance with a P value ≤0.05 taken as significant.*

Data Analysis Procedures: *All data were entered and analyzed through SPSS – Version 17.0). Categorical variables like proximal muscle weakness, bone tenderness, any bony deformities, vitamin D levels and outcome (Vitamin D deficiency) were presented as frequencies and percentages. Numerical variables like age, parity, period of gestational age and Vitamin D level were expressed as Mean ± SD. Effect modifiers were controlled by stratification and this stratification was done on the basis of age, parity and gestational age. Post-stratification chi-square test was applied P ≤0.05 was taken as significant. Results are presented in the form of graphs and tables.*

Results: *Mean ± SD age of pregnant women was 28.19 ± 5.65 years (Ranging from 18-39). Mean ± SD gestational age was 29.21 ± 4.94 weeks (Ranging from 16 to 39). Mean ± SD number of children was 3.85 ± 1.82. Mean ± SD serum level of vitamin D was 24.70 ± 20.68 nmol/ Liter (Ranging from 8 to 85 nmol/ Liter). About 81% (n= 94) patients had serum vitamin D <30 nmol/L (Deficient), 12.97% (n= 15) had 31-80 nmol/L (Insufficient) while hose having normal vitamin D (i-e; 81-220 nmol/L) were only 6% (n= 7). Frequency of vitamin D deficiency was present among 81%. Stratified analysis showed that maternal age & gestational age was non-significant (P value = 0.105 & 0.547 respectively) effect modifiers while the parity was significant (P value < 0.001) effect modifier on the outcome variable.*

Conclusion: *A huge majority of pregnant women have vitamin D deficiency. There is utmost need to address the factors which are responsible for it (like; exposure to sunlight, dietary deficiencies), so as to prevent maternal and fetal complications.*

Key Words: *Vitamin D, Pregnancy complications, Vitamin D deficiency, Fetus, Nutrition.*

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INTRODUCTION:

Vitamin D is a fat soluble vitamin obtained largely from consuming fortified milk or juice, fish oils, and dietary supplements. It also is produced endogenously in the skin with exposure to sunlight. Vitamin D that is ingested or produced in the skin must undergo hydroxylation in the liver to 25-hydroxy vitamin D (25-OH-D), then further hydroxylation primarily in the kidney to the physiologically active 1, 25-dihydroxyvitamin D. this active form is essential to promote absorption of calcium from the gut and enables normal bone mineralization and growth. During pregnancy, severe maternal vitamin D deficiency has been associated with biochemical evidence of disordered skeletal homeostasis, congenital rickets, and fractures in the newborn. Maternal or early life vitamin D deficiency has been linked to increased incidence of several disorders including neonatal craniotabes, prematurity, type-1 diabetes mellitus, schizophrenia, and childhood respiratory infections and wheeze. Normal level of 25(OH)D in humans is 50-70 ng/ml. Vitamin D deficiency is when 25(OH) vitamin D is <30 ng/ml and vitamin D insufficiency is when 25(OH) vitamin D is 21-29 ng/ml.

According to one study Vitamin D sufficiency was noted in 22% insufficiency in 32%, and deficiency in 46%. According to this study, Vitamin D deficiency is high among pregnant urban Pakistani women and their newborns. Recent evidence suggests that vitamin D deficiency is common during pregnancy especially among high-risk groups, including vegetarians, women with limited sun exposure (e.g., those who live in cold climates, reside in northern latitudes, or wear sun and winter protective clothing) and ethnic minorities, especially those with darker skin. Despite abundant sunshine exposure 74% of the pregnant women had vitamin D deficiency in northern India. A study has demonstrated that Vitamin D status progressively worsened in pregnant women from early pregnancy until six months postpartum as the proportion with adequate serum level of Vitamin D fell from 31% at the antenatal visit to 23% after birth and 17% six months later. Infants of mothers with or at high risk of Vitamin D deficiency are also at risk of Vitamin D deficiency.

EPIDEMIOLOGY:

Prevalence of vitamin D deficiency in pregnancy

Vitamin D deficiency during pregnancy is a worldwide epidemic; studies have reported a prevalence that ranges from 18-84%, depending on the country of residence and local clothing customs. In the United States, vitamin D deficiency is estimated to occur in 5-50% of pregnant women. African American women have a much higher risk of vitamin D deficiency, compared with other women because of increased skin pig mentation and low dietary intake. Bodnar, et al., reported the prevalence of vitamin D deficiency and insufficiency in 200whiteand 200 black pregnant women and in the cord blood of their neonates. In African American pregnant women, vitamin D deficiency and insufficiency occurred in 29.2% and 54.1%, respectively, compared with 5% and 42.1% of white pregnant women. Interestingly, 90% of study participants reported that they were taking prenatal vitamins. At delivery, vitamin D deficiency and insufficiency occurred in 45.6% and 46.8% of black neonates, respectively, compared with 9.7% and 56.4% of white neonates.

UNITED STATES OF AMERICA:

In a study from United States of America found that serum 25(OH)D in pregnant women was significantly associated with season of delivery (P=0.0002), average daily D intake (P=0.0008), right upper inner arm pigmentation (P=0.0035), and maternal pre- or early pregnancy body mass index (calculated as kg/m 2) (P=0.0207). The same documented that these factors were significant for cord serum 25(OH)D, which was highly correlated with maternal serum 25(OH)D (r=0.79;P<0.0001). During the year, 54% of mothers and 90% of neonates had 25(OH)D<30 ng/mL (<75 nmol/L). Of women taking daily prenatal vitamin/mineral supplements (400 IU vitamin D), 50.7% had serum 25(OH)D<30 ng/mL (<75 nmol/L). In conclusion, 25(OH)D<30 ng/mL (<75 nmol/L) was prevalent in mothers and neonates across racial groups and seasons, and vitamin D status was associated with both modifiable and non-modifiable risk factors.

Another study from USA evaluated the Vitamin D deficiency and compared pregnant and non-pregnant women. The study found that mean 25-hydroxyvitamin D (25[OH]D) level was 65 nmol/L for pregnant women and 59 nmol/L for nonpregnant women. The prevalence of 25(OH)D<75 nmol/L was 69% and 78%, respectively. Pregnant women in the first trimester had similar 25(OH)D levels as non-pregnant women (55 vs 59 nmol/L), despite a higher proportion taking vitamin D supplementation (61% vs 32%). However, first-trimester women had lower 25(OH)D levels than third-trimester women (80 nmol/L), likely from shorter duration of supplement use.

ASIAN COUNTRIES:

Regarding Asian countries, it was found that in India, vitamin D deficiency was observed in more than 30%, vitamin D status being poor in school children, pregnant women and large cities. Vitamin D status was much better in Malaysia and Singapore, but lower serum 25(OH)D was observed in Japan and China. Rickets and osteomalacia appear quite common in India, but precise data are lacking. Vitamin D status clearly related to latitude and was poor in the elderly in the eastern Ural in Russia, and in Mongolia. The climate in these countries is characterized by short summers and harsh winters. Rickets appears to be common in Mongolia and China, and this is probably due to poor vitamin D status and low calcium intake. Several surveys in India showed poor to moderate vitamin D status, unexpectedly low for the latitude, so close to the equator. A reason might be skin pigmentation. In addition, vitamin D intake is very low in India as well as calcium intake. Endemic rickets has been associated with vitamin D deficiency, low calcium intake and fluorosis. Air pollution probably also plays a role in the large cities. Vitamin D status is better in Malaysia and Japan. In Japan, serum 25(OH) D was positively related to fish consumption.

PAKISTAN:

In a recent study from Karachi Pakistan, determining the prevalence of vitamin D deficiency in Pakistani parturient and their newborns and to assess the correlation between maternal and newborn serum levels of the vitamin D metabolite 25-hydroxy vitamin D3, it was reported that a huge majority of pregnant women (89%) were deficient in vitamin D (serum 25-hydroxy vitamin D3 <30ng/mL). Further the study found a positive correlation between maternal and cord blood 25-hydroxy vitamin D3 levels (r=0.68; P <0.001). Inverse correlations were noted between cord blood 25-hydroxy vitamin D3 and a longer duration of gestation (P=0.003) and with the newborn's birth weight (r=−0.23; P=0.048). Maternal 25-hydroxy vitamin D3 levels were inversely correlated with maternal mean arterial pressure (P <0.020).

VITAMIN D PHYSIOLOGIC COMPONENTS:

Vitamin D is a prohormone that is derived from cholesterol. The nutritional forms of vitamin D include D3 (cholecalciferol), which is generated in the skin of humans and animals, and vitamin D2 (ergocalciferol), which is derived from plants; both forms can be absorbed in the gut and used by humans. Controversy exists as to whether D 2or D3 is more effective in maintaining circulating levels of vitamin D in non-pregnant individuals, and specific data during pregnancy is unknown. Vitamin D occurs naturally in fish and some plants but is not found in significant amounts in meat, poultry, dairy products (without fortification), or the most commonly eaten fruits and vegetables. The Food and Nutrition Board's current recommendation for adequate intake of vitamin D is 200 IU/d for both pregnant and non-pregnant individuals aged 0-50 years. Wild salmon (3.5 oz) provides 600-1000 IU; farmed salmon has approximately 25% of this amount per serving. The same amount of mackerel, sardines, or tuna fish provides 200-300 IU. Cod liver oil (1 tsp) provides 600-1000 IU. One of the few plant sources of vitamin D is shiitake mushrooms, which provide 1600 IU.

Biochemistry of vitamin D and the vitamin D receptor

Metabolism and transport of vitamin D

Vitamin D is a general term for a chemically related family of secosteroid hormones. Vitamin D2 is produced in plants and vitamin D3 is produced in mammals. In humans, vitamin D2, also called ergocholecalciferol, is one-third as potent as vitamin D3, which is also called cholecalciferol. Vitamin D can be obtained from dietary sources but can also be synthesized. Ultraviolet B-light induces cleavage of the B-ring of 7-dehydrocholesterol in skin to yield the secosteroid vitamin D3. Hereafter, "vitamin D" is used to represent either vitamin D2or vitamin D3. Vitamin D and metabolites are hydrophobic, and >99% are transported in the blood bound to vitamin D binding protein (DBP, also known as Gc-globulin) which binds with high affinity in the order 25OHD¼, (OH)2D>1, 25(OH)2D> vitamin D2 or D3. A small fraction (<1%) of these metabolites are also carried by albumin and lipoprotein. DBP-bound vitamin D2and D3 are internalized in the liver and hydroxylation by a mitochondrial P450 enzyme generates 25OHD, which is the predominant vitamin D compound in the circulation. In the renal proximal tubules of the kidney, DBP-25OHD binds to and is internalized by megalin / cubilin, a heterodimericendocytic receptor pair. The 25OHD is released and is hydroxylated by 25-hydroxyvitamin D3 1ahydroxylase, the product of the CYP27B1gene, to yield 1,25(OH)2D.

This kidney generated 1,25(OH)2D is key in mediating the classical functions of vitamin D in calcium homeostasis and bone mineralization. The production of 1,25(OH)2D in the kidney is stimulated by parathyroid hormone and inhibited by fibroblast growth factor 23 and by elevated calcium and phosphate concentrations. Extra-renal expression of CYP27 B1 and 1,25(OH)2D production from 25OHD

occurs in immune cells, the skin, the placenta and other tissues and may contribute to health in both non-pregnant and pregnant women. Importantly, both 1,25(OH)2D and 25OHD are inactivated by CYP24A1, a 24-hydroxylase mitochondrial cytochrome p450 enzyme. This hydroxylase converts both substrates into inactive end products, including 1,24,25-trihydroxyvitamin D and 24,25-dihydroxyvitamin D. As CYP24A1 transcription is induced by 1,25(OH)2D, which provides a negative feedback control on 1,25(OH)2D levels.

REQUIREMENTS FOR VITAMIN D:

The recommended daily allowance of vitamin D for women in the US aged 19–50 years, including during pregnancy, was recently established at 600 international units (IU) per day. This recommendation was based on the amount of intake necessary to sustain blood levels of 25(OH)D above 50 nmol/L for populations with minimal sunlight exposure and was developed solely based on outcomes related to skeletal health. This recommendation was contentious as many researchers have argued that insufficiency should be defined at thresholds of 75 nmol/L or even higher, which would require a much higher intake to reach. A number of recent reviews have covered a rapidly growing body of literature on vitamin D during pregnancy, although few have taken a systematic approach 35 and only a couple have focused on the implications for low-income country settings. To address this gap, we undertook a systematic review of the literature on vitamin D during pregnancy and perinatal and infant health outcomes. The demand for both energy and nutrients is increased during pregnancy. For well-nourished women, only a small amount of additional energy is required because the body adapts to the increased energy requirements and becomes more energy efficient through reduced physical activity and a lowered metabolic rate. Although the average-sized, well-nourished woman requires <10 460 kJ/d (2000 kcal/d) during the last trimester of pregnancy, many women in developing countries restrict their food intake during pregnancy to have smaller infants, on the premise that smaller infants will carry a lower risk of delivery complications.

Table: A. Risk factors for vitamin D deficiency

Northern latitudes, especially winter or spring
Limited sun exposure
Regular use of sunscreens
African American or dark skin
Obesity
Extensive clothing cover
Aging
Malabsorptive syndromes (cystic fibrosis, cholestatic liver disease, inflammatory bowel disease, short gut syndrome)

Table: B. Stages of vitamin D deficiency and adverse effects.

STAGES OF VITAMIN D DEFICIENCY AND ADVERSE EFFECTS			
Stage	**Serum 25(OH)D, ng/mL**	**Maternal adverse effects**	**Newborn infant adverse effects**
Severe deficiency	<10	Increased risk of preeclampsia, calcium malabsorption, bone loss, poor weight gain, myopathy, higher parathyroid hormone levels	Small for gestational age, neonatal hypocalcemia, hypocalcemic seizures, infantile heart failure, enamel defects, large fontanelle, congenital rickets, rickets of infancy if breastfed
Insufficiency	11-32	Bone loss, subclinical myopathy	Neonatal hypocalcemia, reduced bone mineral density, rickets of infancy if breastfed
Adequacy	32-100	Adequate calcium balance, parathyroid hormone levels	None, unless exclusively breastfed
Toxicity	>100	Hypercalcemia, increased urine calcium loss	Infantile idiopathic hypercalcemia

VITAMIN DEFICIENCY DURING PREGNANCY:

The plasma 25(OH)D concentration is a useful vitamin D biomarker because it has a long half-life in the circulation and its concentration is not under tight homeostatic regulation. This biomarker, therefore, reflects vitamin D supply and usage over a period of time. Most researchers agree that the range of the serum concentration of 25(OH)D in a population of healthy subjects is the best indicator for assessing the vitamin D status in patients with a vitamin D-related disease. Traditionally, vitamin D deficiency has indeed been defined as the presence of signs and symptoms that characterize rickets and osteomalacia. Diagnosis requires the use of X-rays, clinical evaluation of bone deformities, bone biopsies, and biochemical tests of metabolic bone disease, such as elevated plasma alkaline phosphatase activity. However, there are key limitations in using 25(OH)D to define vitamin D status. These include (1) the nature of vitamin D as a prohormone, rather than as a nutrient per se; (2) its variability due to many non-nutritional factors (e.g., season, geographic latitude, clothing, institutionalization, use of sunscreen) and physiologic state of the individual (e.g., body mass index, extracellular volume, and vitamin D binding protein (DBP) concentration and affinity); and (3) our lack of understanding of 25(OH)D economy in the body.

The strength of the relation of 25(OH)D to functional outcomes may vary according to outcome and life or reproductive stage. Researchers have studied dose–response relations among vitamin D intakes, serum 25(OH)D concentrations, and functional health outcomes for bone but not for other outcomes. The emerging roles of vitamin D in immune function, autoimmune disorders, cancer, and other chronic diseases (such as diabetes) make the relation of these other functional health outcomes to 25(OH)D concentrations important to understand. Therefore, it is possible, if not likely, that state of vitamin D sufficiency varies throughout the life cycle and, that the current definition of vitamin D deficiency of insufficiency (i.e., based on bone-related disease) is not appropriate for pregnant women.

MATERNAL CHANGES IN BONE AND BONE MARKERS DURING PREGNANCY

Although there are case reports of pregnancy-associated osteoporosis, this appears to be a pathologic condition that occurs among women with preexisting bone disease or that results from inappropriate calcitropic hormonal responses during pregnancy. Ensom et al recently reviewed studies on bone changes that occur during normal pregnancies. Unfortunately, in many studies the final bone measurements were made up to 6 weeks after the birth, when lactation-induced bone changes have already begun to occur. Although studies using biochemical markers of bone formation and bone resorption have been conducted to allow better understanding of bone turnover throughout pregnancy, those studies are difficult to interpret because of changes in renal filtration, hemodilution, and the possibility that the markers are of fetal or placental origin.

Several longitudinal studies that included bone measurements before and after pregnancy showed bone density losses of 2-4%. Decreases in bone density were observed in the spine hip and ultra-distal radius. One study reported an increase in bone density at cortical sites, whereas several other studies reported no changes during pregnancy. The percentage postpartum bone gains among women who did not breast-feed their infants was of a magnitude similar to that of the observed bone loss. Most of the postpartum studies of bone gain did not include non-postpartum control subjects, and it is possible that the bone gain might be a normal, age-related gain. However, there is evidence that the bone changes observed in the postpartum period are not attributable to normal, age-related bone increases. Laskey et al studied 11 non-lactating postpartum women and 22 non-postpartum women of similar age and found a significant increase in bone mass among the postpartum women but no change among the non-postpartum women.

EFFECTS OF MATERNAL VITAMIN D STATUS ON NEONATAL CALCIUM HOMEOSTASIS

In the early 1970s, Purvis et al reported an association between the occurrence of neonatal tetany and the amount of sunlight exposure the mothers had received during the last trimester of pregnancy. Those authors, as well as others, speculated that vitamin D-deficient mothers develop secondary hyperparathyroidism, which leads to transitory hypopara-thyroidism and hypocalcemia among the neonates. Several investigators subsequently reported that infants of mothers with low vitamin D intake during pregnancy had low serum calcium concentrations in cord blood or during the first week of life.

Asian (subcontinent) immigrants to the United Kingdom are at increased risk of vitamin D deficiency. Okonofua et al initially reported low serum 25(OH)D and calcium concentrations and

higher PTH concentrations in maternal and cord samples obtained from 11 Asian mothers, compared with 10 white mothers, at delivery. These authors later reported the results of a similar but larger study involving 43 Asian women and 55 white women who were monitored throughout their pregnancies. They found that PTH concentrations among both Asian and white mothers increased throughout pregnancy. Serum PTH concentrations were inversely associated with serum 25(OH)D concentrations, and Asian mothers had lower 25(OH)D concentrations and higher PTH concentrations than did white mothers. The second study replicated the previous findings of lower serum 25(OH)D concentrations and higher PTH concentrations in cord samples obtained from Asian neonates, compared with white neonates.

ASSOCIATIONS WITH MATERNAL PROBLEMS IN PREGNANCY

Gestational diabetes

There is an association between low maternal vitamin D and gestational diabetes as might be expected from the association with insulin resistance and type 2 diabetes. In a cross-sectional study of 741 pregnant women, the prevalence of severe vitamin D deficiency (<12.5 nmol/L) was found to be higher in those with GDM (44% vs 23.5%) and there was a correlation between insulin resistance and vitamin D level (r¼0.02; P¼0.002).

An Australian study of 307 pregnant women found maternal 25 OHD concentrations inversely related to maternal fasting glucose. The problem with these and many other studies is that it is not clear what role confounding factors such as ethnicity and obesity play in this relationship. Multivariate analysis with its assumption of a linear relationship between the confounders may not be enough to answer this question. The one trial of supplementation with intravenous and oral 1,25-(OH2) D in 12 women with GDM showed no change in glucose but decreased insulin levels following supplementation, suggesting an increase in insulin sensitivity. Not all studies find an association between 25 OHD and GDM.

PREECLAMPSIA:

Preeclampsia occurs more frequently in those women who are vitamin D deficient or become so during the course of pregnancy. In a nested case-control study of women followed from less than 16 weeks gestation to delivery, a 50 nmol/L decline in 25 OHD over the course of the pregnancy increased the risk of preeclampsia by an adjusted odds ratio of 2.4 (95% CI, 1.1–5.4). Low VEGF and increased pro-inflammatory cytokines have been associated with preeclampsia. Vitamin D has been shown to influence their expression which could underlie the association.

One population study examined estimated vitamin D intake and preeclampsia risk and found a reduced odds ratio (0.76, 95% CI 0.60–0.95) for the development of preeclampsia in women with intake 600–800 IU/day compared with less than 200 IU/day. The reduction from supplement intake alone was 27% (OR 0.73, 95% CI 0.58–0.92) for women taking 400–600 IU/day compared with no supplements. There was no association between vitamin D from dietary intake alone and preeclampsia. In a randomised trial of 400 women, 200 were given calcium 375 mg/day and vitamin D 1200 IU/day from 20 to 24 weeks' pregnancy onwards (there was no placebo control). Blood pressure was significantly lower at 32 and 36 weeks in the supplemented group but the incidence of toxaemia (defined as BP>140 mmHg systolic and/or 90 mmHg diastolic with urinary protein>300 mg/24 h) was unchanged.

EFFECT OF VITAMIN D ON THE FETUS AND NEONATE:

Infant size

Low maternal 25 OHD has been correlated with low birth weight, birth length and growth to one year in various studies. In data from the Amsterdam ABCD cohort including 3730 women with a live singleton pregnancy, women with vitamin D deficiency (25 OHD<29.9 nmol/L) had infants with lower birth weights (114.4 g, 95% CI151.2,77.6) and a higher risk of SGA (OR 2.4, 95% CI 1.9, 3.2) compared with women with a 25 OHD>50 nmol/L. A recent nested case-control study of nulliparous pregnant women with a singleton pregnancy who delivered a small for gestational age (SGS) infant demonstrated that in white women there was a U shaped relation between maternal 25 OHD and the risk of a small infant. This relationship was not seen in black women although maternal 25OHD <37.5 nmol/L was more common. In the white women, the lowest risk of an SGA infant was at 25 OHD concentrations of 60–80 nmol/L. Several single nucleotide polymorphisms in the vitamin D receptor are linked to SGA risk.

Infant bones

Decreased skeletal mineralization in utero may be manifested as rickets or osteopenia among newborn infants. However, fetal or congenital rickets among newborns is rare. Case reports of congenitalrickets among newborn infants of mothers with severe nutritional osteomalacia associated with vitamin D or calcium deficiency have been published. Reif et al, in

a case-control study, reported an association between craniotabes, or delayed ossification of the cranial vertex, and maternal and neonatal 25(OH)D concentrations. However, those findings have not been replicated in other observational studies or trials. Although Brooke et al did not find an association between craniotabes and vitamin D status, they did find that infants of mothers who received placebo had larger fontanelles than did infants of mothers treated with vitamin D, which is consistent with impaired ossification of the skull. A study of 256 term infants conducted in China also found possible evidence for a relationship between maternal vitamin D deficiency and impaired fetal bone ossification. Neonatal wrist ossification centers were less likely to be found among infants born in the spring than among those born in the fall (2 of 127 infants, compared with 10 of 129 infants; P 0.05).

Neonatal morbidity

Neonates with low vitamin D may experience hypocalcaemic seizures, particularly if they have any other insult that predisposes to seizures and/or hypocalcaemia. An English study of infants with severe cardiomyopathy related to hypocalcaemia, found a mean infant vitamin D level of 18.5 nmol/L. All these infants had been breast fed. Similarly, a ten year record review at the Children's National Medical Center in Washington DC, found four infants (all exclusively breast fed) presenting with dilated cardiomyopathy and hypocalcaemic rickets, with resolution of the cardiomyopathy with replacement of vitamin D and calcium.

Recommended dietary intakes during pregnancy

In the United States, Australia, New Zealand, and Canada the currently recommended dietary adequate intake (AI) of vitamin D for pregnant women is 200 IU/day while the United Kingdom recommends 400 IU/day. The existing recommendations are the subject of widespread controversy given the evolving concept of vitamin D sufficiency, currently believed to be serum 25(OH)D levels>75 nmol/L, and many recent studies showing a high prevalence of vitamin D insufficiency using lower cut offs.

Supplementation with vitamin D during pregnancy

While a number of vitamin D supplementation trials during pregnancy have been conducted since the early 1980s, interpretation of results is complicated by the type of supplement used and the duration and dose of supplementation. It is clear that either daily or high-dose supplementation during the third trimester of pregnancy has been effective at raising circulating 25(OH)D concentrations compared to controls in all populations studied.

Vitamin D toxicity in pregnancy

Historically, vitamin D supplementation during pregnancy was thought to be a risk factor for supravalvular aortic stenosis (SAS) in infants; this was based on the finding in 1964 of an elevated blood concentration of vitamin D in an infant with this condition. Interestingly, when the case report was published there were no quantitative methods for measuring circulating 25(OH)D. It was later determined that the sporadic association between elevated 25(OH)D and SAS was due to a disease now known as Williams Syndrome, a genetic disorder with a prevalence of 1/7,500 that is characterized by dysmorphic facial features, multi-organ involvement including SAS, and an exaggerated response of circulating 25(OH)D to oral doses of vitamin D.

Health implications

The alarming prevalence of vitamin D insufficiency during pregnancy demonstrated in a diverse range of populations living at various latitudes, the extensive scope of adverse effects to the offspring during development and later in life, and the lack of evidence of toxicity from physiological doses of vitamin D suggest that the current recommendations for vitamin D intake during pregnancy are grossly inadequate. While it may be argued that increased sun exposure would provide a more natural means of achieving better vitamin D status in pregnancy, this method has dermatological ramifications in terms of skin cancer risk and may not be culturally or socially acceptable in some populations. Most prenatal vitamin and mineral supplements that are commercially available in the United States contain 400 IU/day vitamin D as cholecalciferol. Because compliance with prenatal vitamin and mineral intake has been high (70–94%) in several studies of vitamin D status conducted in the United States a sensible public health intervention strategy targeting pregnant women would involve reformulation of prenatal supplements with higher doses of vitamin D.

RESULTS:

The current study was undertaken to estimate the prevalence of vitamin D deficiency among pregnant women presenting to a tertiary care hospital. Sample comprised of 116 pregnant women who had proximal muscle weakness bone tenderness. The mean ± SD age was 28.19 ± 5.65 years with minimum age 18 years while the maximum age was 39 years. Mean ± SD gestational duration was 29.21 ± 4.94 weeks which ranged from 16 to 39 weeks. (Table: 1). Mean

± SD number of children was 3.85 ± 1.82 with minimum number of children 1 and maximum number of children was 8. Mean ± SD serum level of vitamin D was 24.70 ± 20.68 nmol/ Liter with a range from 8 to 85 nmol/ Liter. (Table: 1). More than half of our patients [52.59% (n= 61)] were in third decade of their life. About, a third [32.76% (n= 38)] were in fourth decade of life while only 14.66% (n= 17) were of youngest age group i-e; upto 20 years. (Figure: 1). Distribution of gestational age showed that a huge majority of patients [81.90% (n= 95)] came while the pregnancy was between 25-36 weeks. About, 16.38% (n= 19)] presented while the pregnancy was upto 24th weeks while those presenting within 37th week of gestation or beyond were only 1.72% (n= 2). (Figure: 2).

About one third pregnant women i-e; 31.9% (n= 37) were highly parous having 5-8 children. Those having lesser children than this i-e; 3-4 children were 42.2% (n= 49) while those having upto 2 children were 25.9% (n= 30). (Table: 2). Serum vitamin D level of all patients were evaluated & categorized. It was found that 81.03% (n= 94) patients had serum vitamin D <30 nmol/L (Deficient). About, 12.97% (n= 15) patients had serum vitamin D of 31-80 nmol/L (Insufficient) while the patients having normal serum vitamin D level (i-e; 81-220 nmol/L) were 6% (n= 7). (Table: 3). Thus it was noted the main outcome variable i-e; frequency of vitamin D deficiency was present among 81.03% (n= 94) pregnant women. (Figure: 3). Stratified analysis was performed to evaluate any difference or effect modification of outcome variable. In this regard it was noted that maternal age was a non-significant effect modifier on the outcome variable. With the increasing age, the frequency of vitamin D deficiency among pregnant women increased. (P value = 0.105; Table: 4).

It was also found non-significantly that the gestational age did the effect modification & the frequency of vitamin D deficiency increased with increasing gestational age. (P value = 0.547; Table: 5). Finally; the parity also had effect on the frequency of vitamin D deficiency among pregnant women. The frequency doubled from about 50% among women having upto 2 children to 100% among women which had 5-8 children. This finding was very significant. (P value < 0.001; Table: 5).

Table: 1. Descriptive statistics.

n= 116	Minimum	Maximum	Mean	Standard deviation
Age of the Patient	18	39	28.19	5.65
Gestation duration (in weeks)	16	39	29.21	4.94
Number of Children	1	8	3.85	1.82
Level of Vitamin D (nmol/L)	8	85	24.70	20.68

Figure: 1. Frequency of patients according to maternal age categories. (n=116)

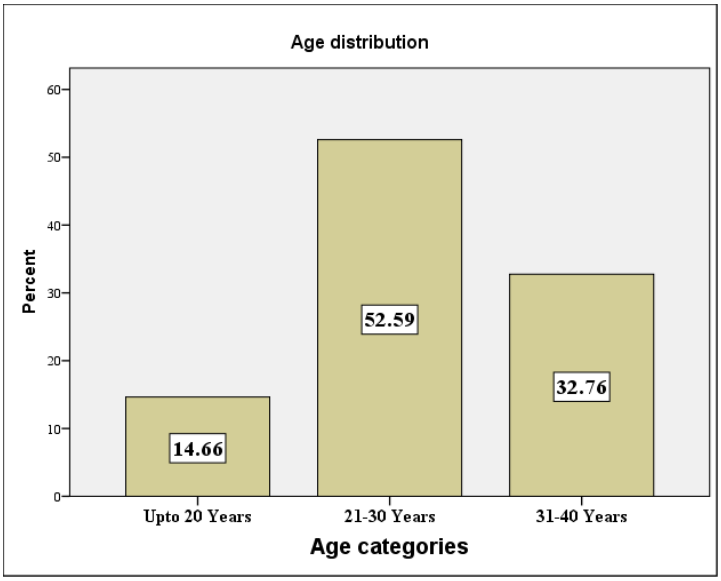

Figure: 2. Distribution as per gestational age (n= 116)

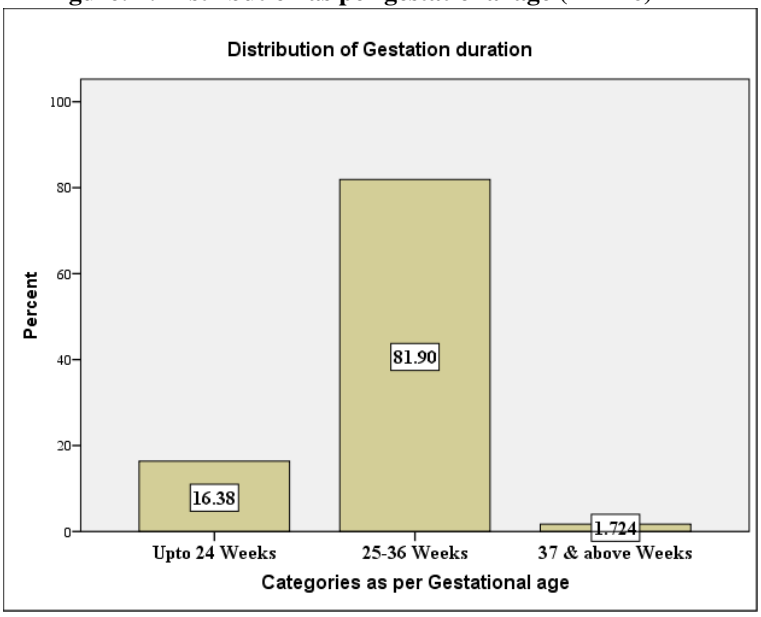

Table: 2. Parity categories.

Number of Children	Frequency	Percent
Upto 2 Children	30	25.9
3-4 Children	49	42.2
5-8 Children	37	31.9
Total	116	100.0

Table: 3. Different categories of serum Vitamin D level

Serum Vitamin D level	Frequency	Percent
Deficient (<30 nmol/L)	94	81.03
Insufficient (31-80 nmol/L)	15	12.97
Normal (81-220 nmol/L)	7	6
Total	116	100.0

Figure: 3. Frequency of vitamin D deficiency among pregnant women (n=116)

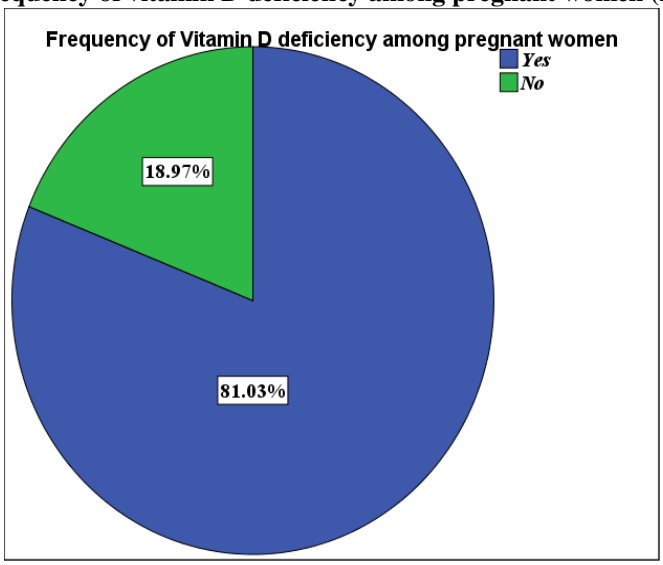

Table: 4. Effect of maternal age on frequency of vitamin D deficiency among pregnant women (n=116)

Age category	Vitamin D deficiency		Total	P value
	Yes	No		
Upto 20 years	13	4	17	**0.105**
	76.5%	23.5%	100.0%	
21-30 years	46	15	61	
	75.4%	24.6%	100.0%	
31-40 years	35	3	38	
	92.1%	7.9%	100.0%	
Total	94	22	116	
	81.0%	19.0%	100.0%	

Table: 5. Effect of Gestational age on frequency of vitamin D deficiency among pregnant women (n=116).

Gestational age	Vitamin D deficiency		Total	P value
	Yes	No		
Upto 24 Weeks	14	5	19	0.547
	73.7%	26.3%	100.0%	
25-36 Weeks	78	17	95	
	82.1%	17.9%	100.0%	
37 & above Weeks	2	0	2	
	100.0%	0.0%	100.0%	
Total	94	22	116	
	81.0%	19.0%	100.0%	

Table: 6. Effect of Parity on frequency of vitamin D deficiency among pregnant women (n=116).

Parity	Vitamin D deficiency		Total	P value
	Yes	No		
Upto 2 Children	17	13	30	<0.001
	56.7%	43.3%	100.0%	
3-4 Children	40	9	49	
	81.6%	18.4%	100.0%	
5-8 Children	37	0	37	
	100.0%	0.0%	100.0%	
Total	94	22	116	
	81.0%	19.0%	100.0%	

DISCUSSION:

The role of vitamin D in bone mineralization and mineral homeostasis is well known. More recently, a role of vitamin D deficiency ina range of disorders has emerged, together with the appreciation that vitamin D deficiency may be widespread. Currently, a pandemic of vitamin D deficiency/insufficiency has been reported globally. Typically, the prevalence of low 25OHD levels has been reported in approximately 36%, otherwise healthy, young adults, aged 18–29 years. If the age criteria are widened or if we consider only the pregnant women, the facts may appear more specific and horrible. During the last decade, there has been growing interest in the prevalence and consequences of vitamin D deficiency during pregnancy. Vitamin D deficiency has been associated with adverse pregnancy outcomes, including pre-eclampsia, gestational diabetes mellitus, intrauterine growth restriction, and preterm birth.

Despite the factthat pregnant women in most countries are encouraged to take a daily prenatal vitamin/mineral supplement containing vitamin D, a disturbingly high prevalence of hypovitaminosis D has been demonstrated among pregnant women in nearly all populations studied. Reported prevalence of maternal vitamin D deficiency at or near term has ranged from 5% to 20% in light-skinned populations to 30% to 70% among dark-skinned or veiled populations living at various latitudes. The current study was performed to assess the burden of vitamin deficiency in patients presenting to a tertiary care hospital where the majority of population is rural, less educated and almost unaware of their health needs. Shaikh Zaid Hospital, the affiliated hospital of Chandka Medical University, is a public sector institution predominantly catering to the needs of middle and low socioeconomic patients thus reflect the rural population of Larkana and its surroundings. Even many patients from Baluchistan are also referred to this hospital. It must be kept in mind that patients presented to our set up were majority illiterate or had very little education. Further because of that, the awareness about antenatal visits and dietary requirement during pregnancy is too low. These conditions are superimposed by the poor socio-economic conditions as about three fourths of our patients belonged to lower income families. This scenario is similarly prevalent among all third world

countries.

The current study found that a huge majority of pregnant women had vitamin D deficiency. The frequency of women with an abnormally low vitamin D was about 81%. This is in concordance with reported figures on vitamin D deficiency in pregnant populations. The 81% prevalence of vitamin D inadequacy among our participants is very high but similar to rates have been reported for other countries. Karim SA, et al., reported that a huge majority of pregnant patients (88%) had Vitamin D deficiency. The 88% of the newborns were also vitamin deficient in this study. International studies have discovered that despite abundant sunshine vitamin D deficiency is common in pregnant women ranging from 65% to 87%. Dror DK, et al reported that 54% of mothers and 90% of neonates had vitamin D deficiency (<30nmol/L).

This deficiency is not confined to veiled women or those with dark skins. In countries with abundant sunlight like India, pregnant women have been shown to have up to 84% prevalence of vitamin D deficiency which correlated significantly with serum 25 (OH) D statuses of their newborns. Therefore; a high prevalence of vitamin D deficiency can be expected in a country abundant in sunshine like Pakistan. Here it can be reiterated that important factor for vitamin D deficiency other than lack of exposure to sunlight is poor diet. In a study evaluating the vitamin D level in general population of Karachi; it was found that the mean serum vitamin D level was 41.1 ±9.6 nmol/L while more than two thirds i-e; 69.9% population was vitamin D deficient. In our study taking the specific population of pregnant women, the value was 24.70 nmol/L. This supports the findings was of our study where only the pregnant women were studied. In a study from India, Goswami R, et al., found that mean serum vitamin D level among pregnant women was 21.9 ± 10.73 nmol/L which coincides with our results. Another study by Namgung R, et al., reported that among pregnant women in South Korea, the mean serum vitamin D level was 24 ± 13 nmol/L. In a large study from USA, it was found that the mean serum 25(OH) D level among all US women aged 13-44 years was 59 nmol/L. This is much higher than that found in current study. This difference is due to above statedreasonsi-e; difference of diet & nutritional status.

The current study also noted that age of women was an effect modifier. As the maternal age increased there was an increase in frequency of vitamin D deficiency. This finding was not significant (P value = 0.105). Some of the similar studies had found some relationship between the age and the vitamin D level. The exact mechanism of this effect is not clear yet. Hossain N, et al., reported that mean age of their patients was 26 ±6.5 years. Another local study by Karim SA, et al., documented that mean ± SD age of pregnant women was 28.16 ± 4.4 years. Dror DK, et al., reported mean age of their patients was 26.4 ± 5.7 years. Our findings were in concordance with these results & mean age of our patients was 28.19 ± 5.65 years.

The current study noted that the patients which presented within third trimester or beyond it had more percentage of vitamin D deficient women as compared to those which presented up till second trimester. This, on one side may be due more consumption of vitamin D by the fetus while on the other hand it may be due to decreased exposure to sun due to more rest in rooms- by the women with an increasing gestation. Though this correlation was non-significant (P value = 0.547) yet it needs to be further evaluated in future studies.

Along with these, a very significant (P value < 0.001) finding of the current study was increased frequency of vitamin D deficiency with increasing parity of pregnant women. Women having >5 children had the highest value and all (100%) of them were vitamin D deficient as compared to those who had 2 or less children in whom the frequency of vitamin D deficiency was nearly half. This not understood why it is so. Most of the reported studies have found the similar results. A recent study from Pakistan done by Hossain N, et al., (2011) found that almost 90% of the pregnant women & their newborns were deficient in vitamin D. Mean parity documented by Dror DK, et al., was 1.2 ± 1.3 children with range of 1-11. Mean parity reported by Karim SA, et al., was 2.22 ±2.19 children while in our study the mean ± SD parity was 3.85 ± 1.82 children which is comparatively higher. This difference may be due to rural population of our study which has higher total fertility. The current study had noted the duration of gestation (at time of vitamin D was evaluated among the pregnant women) had shown an effect on the vitamin D deficiency. Increase in gestational age had increase in frequency of vitamin D deficiency.
Karim SA, et al., reported that with increasing parity there was an absolute and significant increase in maternal hypovitaminosis in their study participants. This finding was in concordance with our study where it was very significantly noted that higher the parity higher was the frequency of vitamin D

deficiency. Other studies from western data have also found similar findings. Thus we can comment that controlling the number of pregnancies is the most important for the health of mother as well as the newborn.

Being a female infant & premature delivery was also a factor of neonatal vitamin D deficiency by currents study like other studies; though it was not the part of this study.

Karim SA, et al., commented that diet insufficient in calcium and vitamin D (P <0.001) and a lack of exposure to sunlight (P <0.007) were associated with vitamin D deficiency in their patients.[7] The current study also noted this relation & found that using veil or covering the body part was associated with more frequency of vitamin D deficiency.

This was clinical study conducted with a cross sectional design. The study has highlighted an important morbidity factor among pregnant women of rural areas of Pakistan. The weakness of this study was that the effect of season and altitude was not included in the study variables. These might have affected the prevalence of vitamin D deficiency in our patients. Besides; the cultural and religious beliefs can also contribute to low vitamin D levels by limiting skin exposure- but it was not evaluated in this study. The study was based on a small sample. Also, the blood samples were collected only once, due to the limited budget of the study. Therefore, we suggest that a larger study with larger sample size, longer duration and serial vitamin D assessment (at different times of the year to study the effect of seasonal variation) with controlling for altitude and cultural practices must be conducted in future so as to understand these factors in better way.

CONCLUSION:

A reasonably high number of pregnant women are carrying their fetuses with critically low serum vitamin D concentrations. This may not be dangerous the mother but the fetus is at higher risk of many complications like rickets, hypocalcaemia and possible enamel defects. Because vitamin D is very important for fetal development and the only source is maternal vitamin D. Low prenatal and perinatal vitamin D concentrations affect the functional characteristics of various tissues of the body, which leads to a greater risk in later life of multiple sclerosis, cancer, insulin dependent diabetes mellitus, and schizophrenia. Therefore; assessment and correction of maternal vitamin D is critical. The current study found that a huge majority of pregnant women have vitamin D deficiency. There is utmost need to address the factors which are responsible for it (like; exposure to sunlight, dietary deficiencies), so as to prevent maternal and fetal complications.

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