Research article

Effect of vitamin D supplementation on fetal growth and development in pregnant womenV. Srilekha¹, B. Vijayalakshmi², I. Yogananda Reddy³, Nayiema Fathima⁴¹Assistant Professor, Department of Physiology, SVS Medical College, Mahabubnagar, 509001 Telangana, India²Professor and Head, Department of Physiology, Saveetha Medical College, Saveetha University, Chennai, Tamil Nadu, India³Professor, Department of Physiology, ESI Medical College, Sanathnagar, Hyderabad, Telangana, India⁴Professor and Head, Department of Gynecology, SVS Medical College, Mahabubnagar, Telangana, India

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ABSTRACT

Introduction and Aim: Fetal growth is a dynamic process that must be monitored in pregnant women to reduce the long-term consequences of fetal anomalies and post-natal effects on their life. The current study was aimed to find out the effectiveness and association of vitamin D on fetal growth during the prenatal period.

Materials and Methods: It was a randomized control trial undertaken in 100 pregnant women who were allocated randomly into two groups based on calcemic state. After giving 6000 IU of vitamin D intervention the fetal growth was measured at the end of 3 months and the variables were obtained before and after the intervention.

Results: The mean difference of fetal weight between groups was 77g was significantly increased to 277g ($p < 0.01$) after 3 months. The mean difference of femur length before intervention was 0.95mm ($p = 0.18$) significantly increased to 3.03mm ($p < 0.01$). Further, the mean biparietal diameter difference was 0.13mm ($p = 0.92$) was substantially increased to 4.77mm ($p < 0.01$).

Conclusion: The current study suggests that the fetal growth variables were significantly increased in post-intervention phases which can be attributed to vitamin D. It has an immense effect on fetal growth which can be supplemented during different trimesters to enhance fetal development.

Keywords: Fetal growth; bicephalic diameter; cholecalciferol; hypocalcemia; fetal growth restriction.

INTRODUCTION

Fetal growth is a dynamic process to be measured and monitored intermittently to define physiological evolution and if any abnormal deformities may lead to congenital anomalies (1). Fetal growth is influenced by various factors including genetic, humoral, environmental, nutritional, uteroplacental, and fetal factors that either delay or accelerates the rate of development (2-4). Various clinical conditions are associated with fetal growth restriction especially preeclampsia and preterm birth (5-7). Therefore, the perinatal rate of morbidity and mortality associated with fetal growth restriction can be reduced by constant monitoring of fetal growth every 3-4 weeks (8,9). Appropriate pharmacological measures must be taken to enhance fetal growth which is essential for non-congenital anomalies. There are a wide variety of elements have been used in clinical practice (10-12). The current evidence has been revealed that umbilical blood flow, transplacental insulin, thyroid hormones, and numerous growth factors play a key role in fetal growth (13). Apart from these traditional known factors, vitamin D also advances organ development in the fetal stage (14). Vitamin D is a fat-soluble vitamin that has a classic function to maintain calcium homeostasis and bone strength. Vitamin D is a prohormone synthesized from cholesterol in the skin and hydroxylated in two positions (1 and 25th OH D) in the liver and kidney

respectively to become active calcitriol. Vitamin D stimulates intestinal calcium absorption and is important in maintaining adequate phosphate levels for bone mineralization, bone growth, and remodeling. It's also believed to be involved in the regulation of cell growth proliferation and apoptosis (programmed cell death), as well as modulation of the immune system and other functions (15,16). Across the world, low maternal vitamin D level is common during pregnancy. Maternal low vitamin D levels immensely influence intrauterine development and lead to long-term health complications (17). There is no fetal production of vitamin D, and it completely depends upon maternal transport to enhance fetal growth and development. Low vitamin D has been associated with preeclampsia, preterm birth, small gestational age (SGA; 18). The association between vitamin D supplementation and increase fetal birth weight and reduced SGA was not elucidated. However, there is a shred of evidence that vitamin D supplementation during pregnancy can immensely influence fetal weight and growth (14). There is paucity in the literature which could not explain the illustrated relationship between vitamin D deficiency and reduced fetal growth during pregnancy. Therefore, the current study was intended to find out the impact of standard, allowable vitamin D supplementation on different variables of fetal growth during pregnancy.

MATERIALS AND METHODS

A Randomized controlled trial was carried out on 100 pregnant women aged between 20-35 years between 2019 and 2020. The study protocol was reviewed and approved by the Institutional Ethics committee of SVS Medical College and Hospital, and an approval number (IEC approval No. 02/2019) was obtained before starting the study. The participants were randomly selected who got pregnancy and gestation age between 1st trimester to 3rd trimester were recruited and allocated into study group (50) and control group (50) based on serum calcium levels. Pregnant women with endocrine disorders, hypertensives, a recent history of major surgeries, and trauma, were excluded from the study. The study protocol's benefits were explained to all participants and clarified their willingness to withdraw from the study. A written informed consent document was obtained from all participants as well as from their guardians and adopted the recommendations of the Declaration of Helsinki guidelines (1975) and later amendments.

All study group participants were interviewed about their pregnancy profile. As they have hypocalcemia, 6000 IU of vitamin D3 was intravenously infused for three months. The dosage

was adopted the recommendations and policies of vitamin D supplementation (20). No adverse effects were reported during the interventional period. Trained nurses carried out all the interventional procedures under the supervision of the fraternity from the gynecology department. The effectiveness of Vitamin D supplementation on fetal growth was measured after three months. The associations of maternal 25(OH)D concentrations during pregnancy on fetal growth were measured the variables include Bicephalic diameter, femur length, and fetal weight by ultrasonography. Later vitamin D levels were also measured using the CLIA method. These analyses enable optimal use of available data, considering correlations within-subjects and assessing both time-dependent and independent associations.

Statistical analysis

The data sets were analyzed using R software and represented as Mean $\pm$ SD values. The normality of data was tested using the Smirnov-Kolmogorov test. As the data sets were skewed, all non-parametric tests were implemented to compare the differences in fetal growth between the two groups. The interclass correlation coefficient was performed to find out the association between desired parameters.

RESULTS

Table 1: The demographic variables of pregnant women in both groups

Demographic variables	Study group	Control group	p- value
Age (Year)	27.6 $\pm$ 3.25	27.4 $\pm$ 3.10	0.73
Height (cm)	159 $\pm$ 5.8	157 $\pm$ 9.5	0.19
Weight (Kg)	74.9 $\pm$ 14.4	66.5 $\pm$ 12.38	0.02*
BMI(Kg/m ²)	29.44 $\pm$ 5.83	27.38 $\pm$ 6.38	0.08
Serum Calcium (mg/dl)	8.13 $\pm$ 0.27	9.49 $\pm$ 0.19	<0.01*
Estimated age (Weeks) Before intervention	16 $\pm$ 4.96	14 $\pm$ 4.30	0.13
Estimated age (weeks) After intervention	28.7 $\pm$ 3.72	27.5 $\pm$ 3.54	0.07
Vitamin D (ng/ml) Before intervention	21.42 $\pm$ 5.06	21.14 $\pm$ 5.17	0.74
Vitamin D (ng/ml) After intervention	33.63 $\pm$ 6.74	24.21 $\pm$ 5.28	<0.01*

Table 2: The difference in fetal weight before and after intervention

Assessment	n	Group				Mean Difference	p-value
		Study group		Control group			
		Mean fetal weight	SD	Mean fetal weight	SD		
Pre intervention	50	1290	329	1217	189	73	0.06
Post intervention	50	1740	346	1463	210	277	<0.001*

Table 3: The difference in femur length before and after intervention

Assessment	n	Group				Mean Difference	p-value
		Study group		Control group			
		Mean Femur length	SD	Mean Femur length	SD		
Pre intervention	50	32.1	3.85	33.05	3.56	0.95	0.18
Post intervention	50	42.04	4.99	39.03	3.91	3.03	<0.01*

Table 4: The difference in biparietal diameter before and after intervention

Assessment	n	Group				Mean Difference	p-value
		Study group		Control group			
		Mean Biparietal diameter	SD	Mean Biparietal diameter	SD		
Pre intervention	50	45.40	7.85	45.53	5.06	0.13	0.92
Post intervention	50	60.30	8.54	55.53	4.52	4.77	<0.01*

* - significant *p* value

The present study was carried out in 100 pregnant women which were allocated into two groups based on the serum calcemic state. The mean age of the intervention group was 27.6 ± 3.25 , and the control group was 27.4 ± 3.10 . All the demographic variables were collected before intervention. Vitamin D levels estimated in both groups were 21.42 ± 5.06 , 21.14 ± 5.17 which was not significant before intervention ($p=0.74$). After 6000 IU of vitamin D intervention and a follow-up of 3 months were significantly increased in the intervention group (33.63 ± 6.74) than the control group (24.21 ± 5.28) ($p < 0.01^*$) as displayed in table 1.

The fetal growth was estimated by ultrasonography and three standard variables were taken to represent fetal growth among all pregnant women. Table 2 shows the mean difference of fetal weight between groups was 77g which was significantly increased to 277g ($p < 0.01^*$) after 3 months. The primary criteria for fetal growth were femur length and the mean difference between groups before intervention was 0.95mm ($p=0.18$) significantly increased to 3.03mm ($p < 0.001^*$) as shown in table 3. Further, the fetal growth was also measured using the biparietal diameter, and the mean difference was 0.13mm ($p=0.92$) which was substantially increased to 4.77mm ($p < 0.01^*$) as displayed in table 4.

DISCUSSION

The current study was aimed to unveil the association between vitamin D supplementation and fetal growth and development. The results were reported in the study were the rate of fetal growth measured using appropriate variables like fetal weight, femur length, and biparietal diameter in pregnant women with vitamin D intervention was significantly higher than the pregnant women in the control group. The exact physiological pathway of vitamins on fetal growth was not fully understood. However, the postulated mechanisms from the literature have been proposed that the active vitamin D induces cell proliferation and genomic enhancement which in turn produce the growth factors that effectively promote fetal growth (20). However, the recommendations of WHO are contrary to denotes based on a Cochrane review despite its latest published data (21,23). Furthermore, Barker's hypothesis on immunomodulatory actions of vitamin D and is evidenced by the diseases in adult life that might be caused due to nutritional insults in perinatal life (24). The vitamin D synthesis in pregnant women is completely dissimilar to non-

pregnant women. Vitamin D levels are progressively increased in 1st trimester and attain a peak level of threefold which would cause severe hypercalcemia in a non-pregnant woman (24). But the same vitamin D level during pregnancy is essential to modulate inflammatory reactions and cellular proliferation of healthy fetal tissues. Vitamin D also controls endothelial activity which in turn maintains vascular integrity. This is evidenced by lower vitamin D levels are associated with cardiovascular comorbidities (25). Skeletal growth of fetus mainly depends on calcium deposition, and synthesis of the matrix which is also promoted by the direct effect of activated vitamin D. Maximum fortification of pregnancy consequences, including preeclampsia in the mother and asthma can be reduced by the supplementation of vitamin D at least 4000 IU (26). The mechanisms remain mysterious, but it is to be expected that epigenetic in utero changes elicited by vitamin D administered to the pregnant women instruct efficient changes in the fetus. It ensures these supplements are safe from the studies carried out in the last two decades, and not even a single argumentative event has been observed. Further, supplementation lies within the safe intake level as defined by The Endocrine Society. However, the role of vitamin D supplementation in non-classical, immune lines remains to be encountered and substantiate by recommendations and public health policies for pregnant women (27). Our study has shown that 6000 IU of intravenous vitamin D supplementation has considerably improved the fetal variables to indicate growth is promoted partly by vitamin D. The results of the current study were shown the same trend with literature that can be recommended to the pregnant women.

Limitations

There are certain limitations to the current study. The sample was less to make a generalized conclusive statement, and we had taken only a few parameters to represent fetal growth. We could measure fetal growth only at once after intervention which could be one of the limitations of our study. Further studies are warranted to make fruitful results using the same methodology with more sample size by conducting longitudinal cohort studies.

CONCLUSION

The present study outcome reveals that pregnant women after supplementation of vitamin D can effectively improve fetal growth in all dimensions.

Therefore, vitamin D has a growth-promoting effect, especially in prenatal life. This can be implemented in rural areas where they do not have proper facilities to take care of intrauterine growth.

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CONFLICT OF INTEREST

The corresponding author declares on behalf of all authors that there is no potential conflict of interest for the publication of this article.

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