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Serum 25 hydroxycholecalciferol levels throughout pregnancy - A cross-sectional study in South Indian Pregnant Women

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ABSTRACT

Vitamin D deficiency has been reported worldwide. It has been reported at suboptimal levels in gestation. The levels vary during various trimesters of pregnancy. This article focuses on the gestation week wise variations observed in the serum cholecalciferol levels during gestation. 100 venous blood samples were collected from singleton, non-smoking pregnancies. The samples were collected in the summer and winter seasons during various weeks of pregnancy. The samples were collected randomly in patients who were not supplemented with vitamin D. The serum cholecalciferol levels were observed to be deficient during the first trimester (below<30 ng/ml), there was an increase in the vitamin D levels in the second trimester (levels<30 ng/ml). During the third trimester, the levels increased gradually. The ratio of cases deficient during the first trimester was higher when compared to the second and third trimesters. The serum cholecalciferol levels remain deficient due to the foetal organogenesis in the first trimester. The serum 25 hydroxy cholecalciferol levels are compensated with the development of the placenta. During the second trimester, it gradually increases and reaches sufficient limits during the third trimester.

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INTRODUCTION

Vitamin D status is usually estimated by measuring the level of plasma 25(OH)D. Vitamin D is produced by the UV action on the 7- dehydrocholesterol levels in the skin. 25 hydroxy cholecalciferol (calcidiol) storage forms of vitamin D.

Serum 25 hydroxycholecalciferol estimation shows the exact vitamin D status of a person. This calcidiol is activated to calcitriol by 1 alpha-hydroxylase enzyme in the kidney. Calcitriol (1,25dihydroxycholecalciferol) which is the active form of vitamin D, acts as an immune system modulator by providing an effective physical barrier and strengthening both innate and adaptive immunity. It maintains epithelial barrier integrity by restoring tight junctions, gap junctions, and adherens junctions. (Zhang *et al.*, 2013)

Deficient levels of 25 hydroxycholecalciferol affect the vitamin D status of an individual. Obstetric endocrinology is an area with good scope for research. Pregnancy is an altered physiological state with hormonal level variations.

Immunomodulation needed to prevent the heterogenous foetus from maternal immune auto rejection. This is achieved by a specialised group of T

cells known as T regulatory cells. These cells monitor the immune system by suppressing immune functions. They prevent autoimmunity. The gravid endometrium is a niche for T regulatory cells. These cells are observed to be increased during pregnancy than in a non-pregnant woman.

Vitamin D is known for binding in the non-codon region of FoxP3 cells and increasing the production of T regulatory cells and IL -10, which controls inflammation. Hence Vitamin D has been known as immunomodulator (Khemka *et al.*, 2020). Dietary supplements play a very important role in pregnancy. Iron, folic acid vitamins, minerals are supplemented during pregnancy, while vitamin D levels also need to be monitored. This article will provide an insight on the week wise serum cholecalciferol levels in gestation.

MATERIALS AND METHODS

The study was conducted after getting approval from the institution scientific review board and human ethical clearance. The participants were pregnant women aged between 20-40 years, singleton pregnancy without a history of smoking. After getting informed consent, venous blood samples were collected from 100 pregnant women without any supplementation for vitamin D. The samples were collected from week 7 till week 38 weeks.

The participants identified with deficient or insufficient levels of 25 hydroxycholecalciferol (calcidiol) was supplemented by the obstetrician. The participants supplemented with vitamin D were not repeatedly assessed. Multiple samples in the same gestational age were collected. Under aseptic conditions, 5ml of venous blood from antenatal mothers were taken during their routine check-up. The blood collected was centrifuged, and serum was separated using REMI 2500-3000 RPM/per minute. The sample was centrifuged for 10-15 minutes. The serum was utilized for estimation of vitamin D. The estimation was done using the Chemiluminescence (CLIA) method.

OBSERVATION

The serum vitamin D values were estimated from the 7th week of gestation till the 38^{th} week. We were unable to get serum samples earlier than 7 weeks. The values of vitamin D and serum calcium were tabulated according to the gestational age. It was vividly evident that the serum values of vitamin D levels during the first trimester was insufficient or deficient the mean value was 6ng/ml. 25.23 ng/ml in the second trimester. During the third trimester mean value was 26.11ng/ml. The serum vitamin D status in the first trimester was observed to be lower when compared to second and third-trimester participants. Serum Calcium levels were observed to be normal in all three trimesters.

The week wise average values were tabulated for study purposes (Table 1)

We were unable to procure serum samples from week 1 to week 6. The tabulated values will be a guideline for treating pregnant women. Deficient participants were supplemented with vitamin D by the obstetrician and excluded from the study. The study aimed to assess the levels of serum vitamin D in pregnant south Indian women before supplementation.

DISCUSSION

Vitamin D demand of pregnant women exceeds that of a non-pregnant woman of the same age group. During the first trimester, the foetal demand increases during organogenesis. (Abrams, 2007) The foetus accumulated 2-3mg/dl of calcium in the bones. The maternal source of calcium is intestinal absorption. The foetal depend on the maternal sources for its skeletal growth. Mineralisation and calcium absorption by the foetus is maximum during the third trimester. (Ritchie *et al.*, 1998; Cross *et al.*, 1995)

The first-trimester average serum 25 hydroxycholecalciferol level was 6 ng/ml, which is deficient. While 25.23(insufficient) in the second trimester, gradually increasing to 26.11ng/ml (insufficient) in the third trimester. The serum values were collected all around the year. 90% of the South Indian pregnant women had insufficient serum 25 hydroxycholecalciferol levels. The foetal skeleton accumulates 30g of calcium in the third trimester (Mulligan *et al.*, 2010). Third-trimester vitamin D status also influences the 6-8 weeks postnatal life of a neonate, after which it's the food supplementation given. Human milk is not a rich source of vitamin (Hollis *et al.*, 1981).

Levels were lower during the first trimester but gradually improved during the third trimester. In the previous studies conducted 1,25(OH)2D (activated form calcitriol) levels in plasma was observed to be 2 fold increase that the pre pregnancy state. It gradually increases from first trimester reaches maximum levels in third trimester and then returns to normal levels during lactation. (Cross *et al.*, 1995)

This clearly states that the activated form or Calcitriol 1,25, (OH)2D is responsible for maintaining T regulatory cell count in the gravid endometrium

Table 1: The week wise average values

Gestation age	Serum calcium	Average Serum 25 hydroxycholecalciferol levels in ng/ml	nmol/L
Week 7	8.4	17.4	43.5
Week 8	8.9	16.5	41.25
Week 9	8.3	12.5	31.25
Week 10	9.3	6.2	15.
Week 11	10	22.5	56.25
Week 12	9	6	15
Average first trimester	8.983333	13.5166667	33.7083333
Week 13	8.1	27	67.5
Week 14	9	27	67.5
Week 15	8.6	23.8	59.5
Week16	9.1	25	62.5
Week 17	9.4	26	65
Week 18	9.3	26.3	65.75
Week 19	9	25.3	63.25
Week 20	9.15	28	70
Week 21	9	20.4	51
Week 22	9.07	25	57.5
Week 23	9.65	23	110.185
Week 24	9	26	65
Average of the second trimester	9.03083333	25.2333333	67.0570833
Week 25	8.6	24	60
Week 26	9.35	33.5	83.75
Week 27	9.8	26.3	65.75
Week 28	9.7	30.4	77.87
Week 29	9	35	86.5
Week 30	9.3	23.8	59.5
Week 31	8.5	22.5	56.25
Week 32	9.8	11.6	29
Week 33	9.8	21.7	54.25
Week 34	9.2	26.3	65.75
Week 35	9	23.8	59.9
Week 36	9.8	21.7	54.25
Week 37	8	22	35.5
Week 38	9.2	43	107
Average serum cholecalciferol levels in the third trimester	9.2	26.11	65.27

and to sustain pregnancy in the early stages. (Wilson *et al.*, 1990) It is also needed for foetal skeletal development. (Bikle *et al.*, 1984)

During the second trimester, the levels of calcitonin increase two folds compared to the first trimester and at term. This is a protection against the maternal skeleton from excessive resorption for calcium. Thus serum calcium levels are maintained within normal limits even with deficient 25 hydroxycholecalciferol levels. (Taylor *et al.*, 1975)

During the third trimester, the foetal demand as well as maternal demand increases. The foetal bone mineralisation occurs in the third trimester. (Hong *et al.*, 2005) Osteoprotegrin levels have also been shown to be higher in the third trimester of pregnancy than in the first trimester of pregnancy. Osteoprotegerin acts as a decoy receptor for RANK ligand (Receptor Activator of Nuclear Factor-kappaB Ligand" (RANKL), which is an essential factor for bone remodelling) and prevents osteoclastic activity in the maternal skeleton from excessive resorption for serum calcium level maintenance. (Uemura *et al.*, 2002; Agudelo-Zapata *et al.*, 2018)

The placental secretion of 25 hydroxy cholecalciferol also helps to maintain its levels within sufficient limits. The study shows that the third-trimester levels of 25 hydroxycholecalciferol levels is observed to be higher when compared to the first and second trimester.

CONCLUSION

The serum 25 hydroxycholecalciferol levels in gestation varies in different trimesters. It's comparatively low in the first trimester while it gradually increases in the second trimester. The levels reach highest in the third trimester. The serum 25 hydroxycholecalciferol levels maintain 1,25 OH 2D (calcitriol) levels within normal limits even in pregnancy. Calcitriol is a key factor to influence the immune regulatory mechanism and helps in sustaining a pregnancy. Deficient calcitriol levels may induce spontaneous recurrent abortions in early pregnancy. Calcitriol is also crucial in maintaining serum calcium levels. It's an important cofactor for intestinal calcium absorption and conversion. Deficient calcitriol levels may induce maternal bone resorption as a compensatory mechanism to meet out the serum calcium maternal demands and foetal demands. Hence maintaining normal 25 hydroxycholecalciferol levels is important to prevent pregnancy complications. Deficient 25 hydroxycholecalciferol has also been associated with an increased renin-angiotensin-aldosterone mechanism with increased levels of proinflammatory cytokinin production. This increases the chances of pregnant women getting exposed to respiratory infections, especially COVID 19. The susceptibility and severity of COVID -19 infections are more in pregnancy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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