Manuscript Number :VTE-2020-09
Type: Commentary Article
Received date: 17July, 2020
Accepted date: 18 July 2020 P
ublished date: 31July, 2020

Title: Vitamin D levels of the term Small for date newborns at birth and at 3 month of age after vitamin D supplementation with 2 different doses 400IU v/s 800IU- A Randomized control trial

Authors: Syed Manazir Ali[1], Jyothi Naik[1] Uzma Firdaus[1], Jamal Ahmad[2]
[1]Department of Paediatrics, [2]Department of Endocrinology, JNMC, AMU, Aligarh

Abstract

Introduction: Daily supplementation of vitamin D seems to b the most appropriate way to prevent its deficiency and its manifestations. Many studies have suggested Vitamin D Defiency in New born, but we do not have any standard guidelines for Vitamin D supplementation in these patients. The objective was to study the effect of vitamin D supplementation in a dose of 400IU v/s 800IU on vitamin D status of healthy small for date term newborn babies who are exclusively breast fed for 3 months.

Methods: In this randomized trial healthy term small for date babies (n=44 in both groups) who are exclusively breast fed till 3 months were given oral vitamin 400 IU in Group A and 800 IU in Group B. Serum Vitamin D was estimated at birth and at 3 months of age. Vitamin D defiency was defined as <20ng/ml, Insuffiency as 20-30ng/ml and >30ng as Normal value.

Results: Of the total of 50 babies enrolled in both groups 6 babies were excluded due to non compliance and dropouts. The Vitamin D levels were comparable at birth 17.82±6.5ng/ml in group A and 17.54±7.4ng/ml in Group B. At 3 months the Vitamin D level increased to 31.43±6.6ng/ml and 34.06±8.2ng/ml in Group A and Group B respectively. There was no significant difference between the 2 groups (p value 0.101).

Conclusion: Daily Vitamin D supplementation of 400IU seems to be sufficient for small for gestation (SGA) babies who are exclusively breast fed.

Key words: Small for Gestation, Vitamin D deficiency, Supplementation.
Received: 17July, 2020; **Accepted:** 18July, 2020; **Published:31**July, 2020

Address for Correspondence: Prof S.Manazir Ali, Neonatal section of ,Department of Pediatrics, JNMC, AMU, Aligarh, UPMobile No:+91-9837142555, E mail :manazir1958@yahoo.com

INTRODUCTION

Vitamin D is the essential precursor of 1, 25-hydroxyvitamin D, the steroid hormone required for calcium absorption, bone development and growth in children. During the first 6-8 wk of life, the vitamin D status of infants is determined by the vitamin D levels at birth. Breast milk concentration of vitamin D is low (<20 IU/l) and is inadequate for the needs of the growing infant[2]. Vitamin D in breast milk relates to mothers vitamin D intake, skin pigmentation and sunlight exposure[3].

Vitamin D deficiency with a resurgence of rickets is increasingly being reported in infants and toddlers from various parts of the world, especially from temperate regions and among African American babies. Rickets and hypocalcemic seizures due to vitamin D deficiency in exclusively breastfed young infants have been recently reported from southern India. There are a few reports of vitamin D deficiency among pregnant women and cord blood of their small for date babies and breastfed young infants from India.

Daily vitamin D supplementation is considered to be the most appropriate way to prevent vitamin D deficiency and its clinical manifestations such as rickets, growth failure, lethargy, or irritability[13, 14]. Guidelines for vitamin D supplementation in the first year of life differ from country to country and have been modified several times during the past decade[15]. The American Academy of Pediatrics recommends a daily intake of 400 IU vitamin D for all infants, children, and adults. On the other hand, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommend daily supplementation of 800 to 1000 IU/ day for preterm infants in the first months of life. The World Health Organization recommends 400 IU to 1000 IU/ day of vitamin D supplementation in low birth weight infants.

Even though many studies in India suggest deficiency of Vitamin D in Newborns we do not have any standard guidelines for Vitamin D supplementation in these patients. Many studies suggest daily oral supplementation of 400 IU for term babies and 800 IU for pre term babies. The recommended dose of Vitamin D of 400 IU seems to be inadequate to normalize the serum Vitamin D level. The effective dose of Vitamin D to prevent its deficiency is yet to be defined for Indian population. We did a randomized trial comparing two different regimes of oral Vitamin D supplementation (i.e.400 IU vs. 800IU) on serum vitamin D levels in exclusively breast fed term Small for date infants at 3 months. To the best of our knowledge no similar study has been done in this part of the country. The main objective of the study is to evaluate the level of Vitamin D in small for date newborns and compare the effect of 800 IU & 400 IU of Vitamin D supplementation on Vitamin d levels.

Material& Methods

SUBJECTS AND SETTING:

We conducted this prospective randomized trial at neonatology unit, department of paediatrics in collaboration with department of endocrinology JNMCH, AMU, Aligarh, over a period of two years (September 2015 to September 2017). The subjects included were new born babies who had all the following features like healthy term small for date babies born of normal delivery (gestation period between 37-41 weeks or 259-293 days),

birth weight <2500 grams, who are exclusively breast feed for 3 months and babies who were given daily supplementation of oral vitamin D.

Preterm babies with birth weight </=2500 grams, liver renal intestinal problems, on medications like Anticonvulsants Glucocorticoids, mothers having any systemic diseases, malignancy were excluded. Gestational age was calculated by using either first day of last menstrual period or modified New Ballard score. Informed written consent was obtained from the parents or legal guardians before enrolment. The study was approved by the Institutes Ethics Committee (JNMC, AMU, Aligarh). The trial has also been registered at Clinical Trial Registry of India (CTRI).

RANDOMIZATION:

Babies in both the groups were randomly assigned to receive two oral doses of Vitamin D at a dose of 400 IU or 800 IU /day. We used computer generated random numbers to allocate infants to one of the study groups with a fixed block size of 4, which was maintained by a colleague not directly involved in this trial. Allocated interventions were kept in a sealed opaque envelope which was opened at the time of randomization. Subjects were allocated to either of the two interventions in order of their enrollment for study.

STATISTICAL ANALYSIS:

The continuous variables were expressed as mean, standard deviation and confidence intervals (95% CI) frequency and range .Independent sample T test was used to compare means of variables of 2 groups of cases. Paired sample T test was used to compare means of 2 variables for a single group (at birth and at 3 months). P value <0.05 was taken as significant. Analysis was performed by intention to treat.

SAMPLE SIZE:

In an earlier study by Natarajan et al ,2014 The prevalence of vitamin D deficiency in 800 IU was significantly lower than the 400 IU group at 40 wks GA (38.1%v/s 66.7%);relative risk of 0.57% , At 3 months (12.5% v/s 35% relative risk :0.36). Assuming an estimate of prevalence of deficiency of 75%in 400 IU group we needed to enroll 35 babies per group to detect a decrease in prevalence of vitamin D deficiency after supplementation with 800 IU /day with a power of 90% and an alpha error of 0.05%We planned to enroll 50 babies per group to account for loss to follow up.

BRIEF PROCEDURE:

This was a prospective randomized study done over a period of two years (from Sep 2015 to Sep 2017) at Neonatology unit, Dept of Pediatrics in collaboration with Dept of Endocrinology JNMC, AMU, Aligarh. 130 New born SGA Babies after delivery were evaluated for the study of which 100 babies were recruited as per inclusion and exclusion criteria. These 100 Eligible SGA babies were randomly divided into two groups.

Group 1: Babies who received single oral Vitamin D dose 400 IU/day for 3mths

Group 2: Babies who received single oral Vitamin D dose 800 IU/day for 3mths

A written and informed consent was taken from Parents/ legal Guardians Detail Antenatal History, Postnatal history and Examination findings were recorded. The birth weight, Length, Head circumference and Chest Circumference was documented at birth. About 3 ml of cord blood sample from the neonates within 48 hours of Delivery and refrigerated at about -20^{o} in the department after labeling.

The mothers of both the groups are advised to exclusively breast feed the child and inform any deviation from it. They were advised to give daily oral supplementation of 400 IU or 800IU of Vitamin D suspension in the bottle as per the allotment. The drug was Oral Vitamin D suspension (D pura SANOFI India Limited 1ml=800IU). About 0.5ml was administered for the group 1 and 1ml was administered for the group 2. It was administered once daily to infant either directly or mixed with expressed breast milk. Mothers were counseled for exclusive breastfeeding at discharge .Compliance of the Vitamin D intake was checked with return of empty bottles at follow up and telephonically during intervention periods.These infants are followed up upto 3 months when they visit for routine Immunization. Detailed history about any illness and breast feeding were recorded. Repeat examination was done at the follow up and Anthropometric measurements were recorded as done at enrolment.

Another 3 ml of venous blood sample was be collected from Infants and refrigerated after labeling till analysis was done

The laboratory technician conducting the test was unaware of the treatment allocation group and whether the levels were assessed pre- or post-supplementation with vitamin D. All These blood Samples will be subjected for estimation of serum vitamin D level. Total circulating 25(OH)-D were assayed on Access 2 immunoassay system (Beckman Coulter) using chemiluminescence in the laboratory of Rajiv Gandhi Centre for endocrinology, AMU. The assay measures total 25(OH) vitamin D with equimolar measurement of 25(OH) vitamin D2 and 25(OH) vitamin D3

The values of the serum Vitamin D levels was classified as follows[29]

- Deficiency: <20ng/ml
- Insufficiency: 20-30ng/ml
- Sufficiency: >30ng/ml
- Toxicity: s>150ng/ml

RESULTS

Of the 130 small for Gestation new born babies considered during the study period, After excluding 30 patients on the basis of prespecified criteria, we enrolled 100 SGA babies in the study (Fig 1).. Study intervention was initiated in 100 infants after randomization. Of these 6 patients were excluded from the study due to poor compliance, not exclusively breast feed and loss of Follow up. So at the final follow up there were 44 patients in both groups for final analysis.

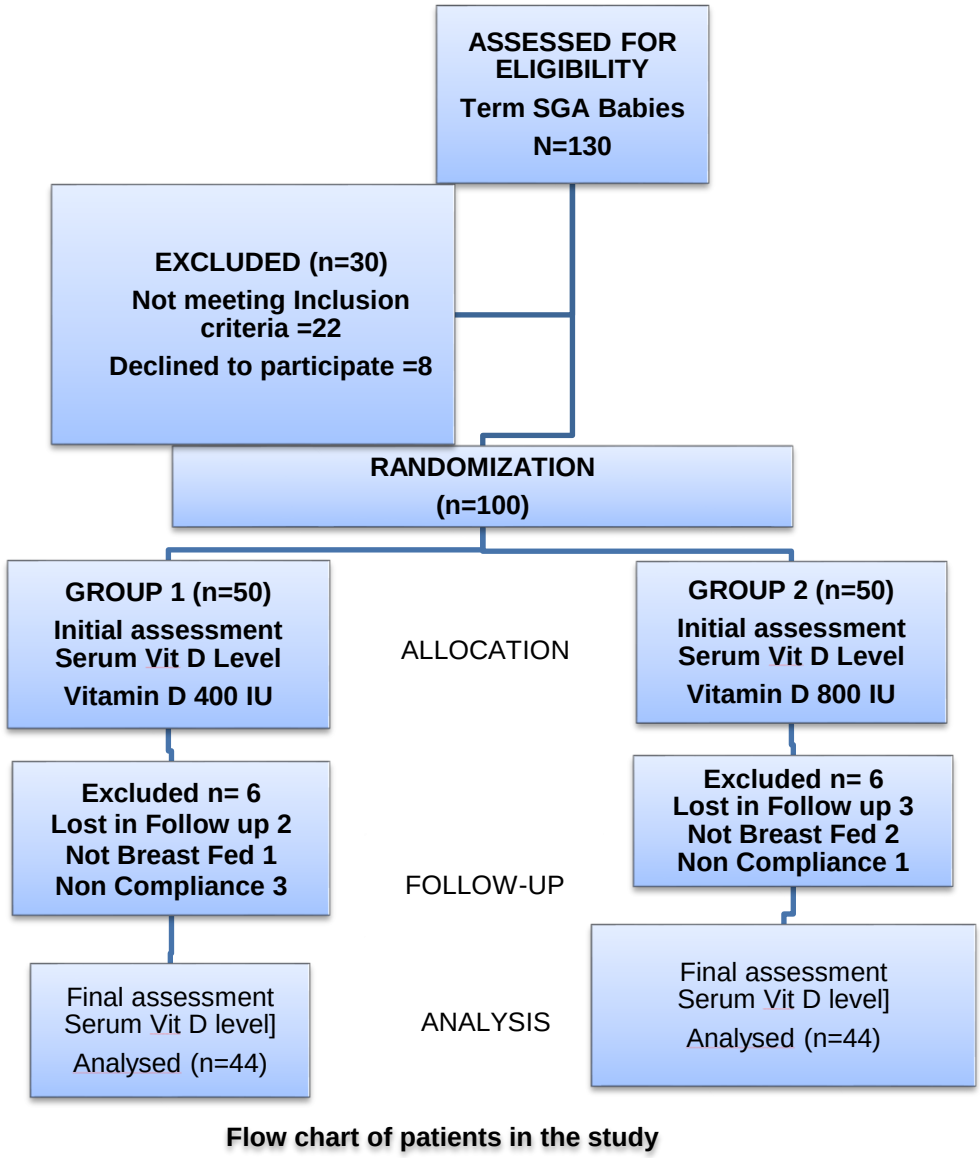

Figure 1. Showing flow chart of patients in the study

Clinical Parameters

The ratio of male and females in both the groups is almost equal (Fig 2). The Mean age of the mother at delivery in both the groups are comparable and not significant (Fig 3). The maen age of mothers was 24.9±2.9 years in group 1 and 25.7±3.9 years in Group 2.

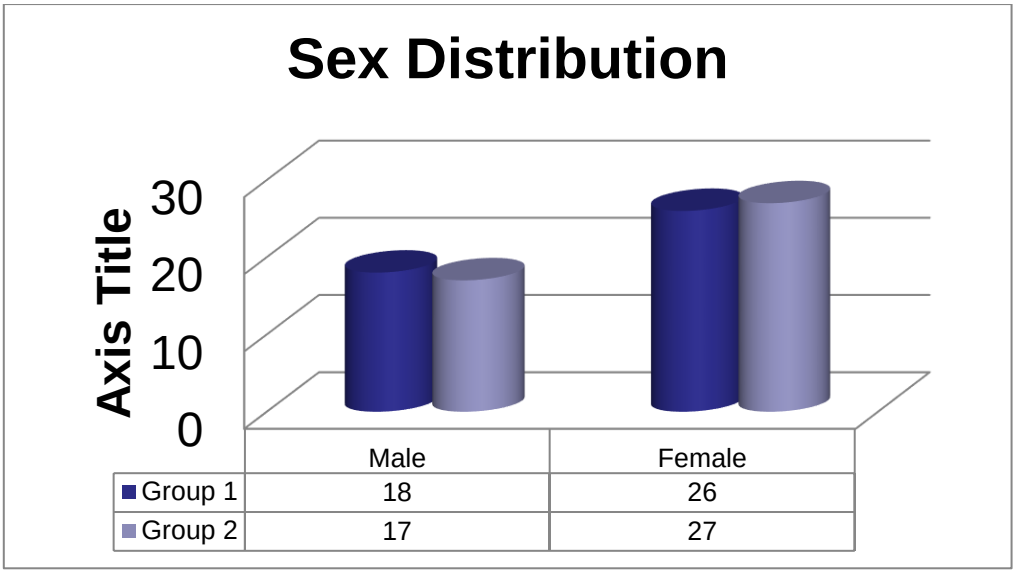

Figure 2. Showing Sex distribution in both groups

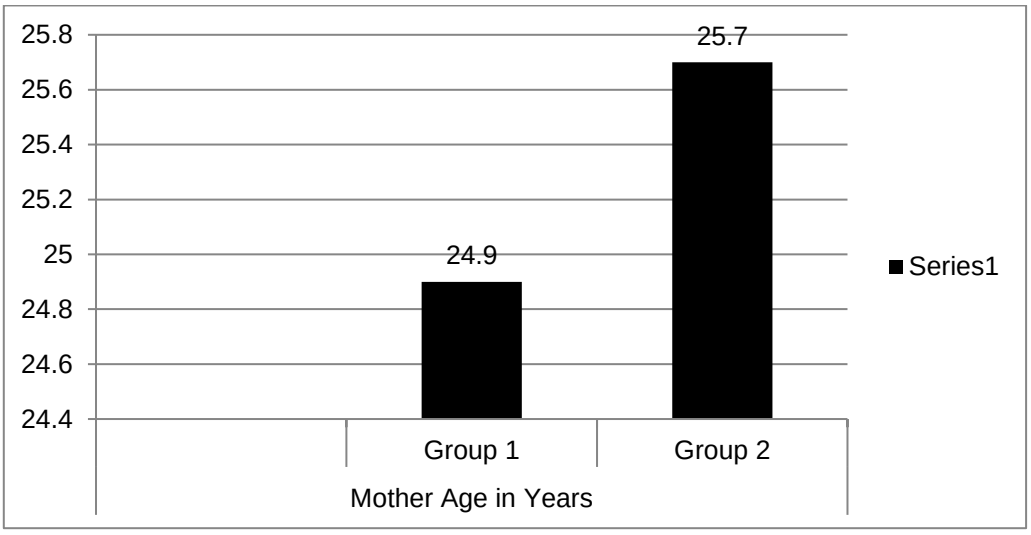

Figure3. Showing Mother age (mean) in both the groups

There was more number of caeseration sections than normal deliveries in Group 1(23:21)) when compared to Group 2 (11:33). This seems to be an incidental finding may need more evaluation (Fig 4).

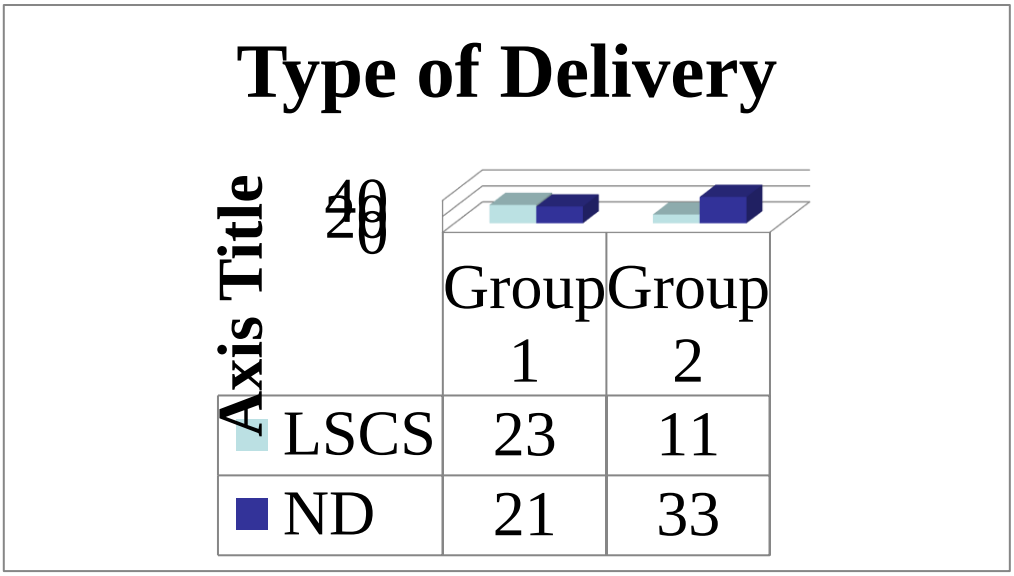

Figure 4. Showing the Type of Delivery

The clinical parameters at birth and at 3 months are comparable except the Weight and Length which shows statistically significant improvement in group 2 (Table 1 and Table 2).

	Group1 (n=44)	**Group 2 (n=44)**	**P value**
Weight (in Kgs)	2.14 ± 0.28	2.12 ± 0.29	0.742
Length (in Cms)	46.2 ± 2.9	45.6 ± 3.1	0.351
Head Circumference (in Cms)	31.4 ± 2.0	31.4 ± 2.4	1
Chest Cicumference (in Cms)	29.6 ± 2.2	29.7 ± 2.3	0.835

Table 1. Showing Clinical parameters at Birth

	Group 1 (n=44)	**Group 2 (n=44)**	**P value**
Weight (in Kgs)	3.24 ± 0.31	3.44 ± 0.39	**0.009**
Length (in Cms)	50.3 ± 3.3	48.6 ± 3.5	**0.021**
Head Circumference (in Cms)	35.2 ± 2.4	34.3 ± 2.5	0.088

Chest Cicumference (in Cms)	31.7 ± 2.3	32.1 ± 2.4	0.427

Table 2.. Showing Clinical parameters at 3 months

Lab Parameters

On comparison of Vitamin D levels between the groups, the maen Vitamin D level at birth was was 17.81 ± 6.51 and 17.54 ± 7.46 ng/ml in Group 1 and Group 2 respectively. After supplementation of Vitamin D for 3 months The mean Vitamin D level was 31.43 ± 6.60 in Group 1 and 34.06 ± 8.21 in Group 2. On comparing between groups there was some increase in value of Vitamin D but it was not statistically significant (Table 3).

	Group 1 (n=44)	**Group 2 (n=44)**	**P value**
At Birth	17.81 ± 6.51	17.54 ± 7.46	0.856
At 3 Months	31.43 ± 6.60	34.06 ± 8.21	0.101

Table 3. Comparing Vitamin D levels in both groups

The status of Vitamin D at birth showed that in Group 1 all patients (n=44) were Deficient or insufficient. Where as in group 2 42 patients were Deficient or insufficient and 2 patients were normal. At 3 months more than 60% of patients had normal Vitamin D level and about 33% had insuffient levels of Vitamin D in both groups. Two patients in both groups were deficient at 3 months.

	Group 1 (n=44)		**Group 2 (n=44)**	
	At Birth	**At 3 Months**	**At Birth**	**At 3 Months**
Deficiency	27 (61.4%)	2 (4.5%)	29 (65.9%)	2 (4.5%)
Insufficiency	17 (38.6%)	14 (31.8%)	12 (27.3%)	15 (34.1%)

Sufficiency		28 (63.6%)	3 (6.8%)	27 (61.4%)

Table 4. Showing status of Vitamin D levels in both groups

DISCUSSION

This RCT was planned to determine the dose of Vitamin D required in SGA babies. The Vitamin D level was below baseline in both the groups at birth (except 3 babies had normal levels in Group 2). This is comparable to other studies and similar to Pre term babies with Low Vit D levels at birth. This may due to high prevalence of Vitamin D deficiency in the Mothers as suggested in many other studies.

Vitamin D level was significantly improved in at 3 months when compared to at birth in both the groups (Only 2 patients were deficient in both groups at 3 months). This improvement at 3 months could be attributed solely to daily supplementation of vitamin D. All our patients are exclusively breast fed, Breast milk probably is a poor source of vitamin due to the high prevalence of VDD in lactating mothers in India.

Denovo synthesis from sun exposure is not a reliable source of vitamin D in infants. More than one-third of infants in the both groups were still had vitamin D insufficiency at 3 months. This may confer that either 400 or 800 IU of vitamin D daily may be inadequate in achieving sufficient vitamin D levels by 3 months. This finding was probably due to the duration of vitamin D supplementation being not long enough.

To the best of our knowledge no similar study has been done, As it was done on SGA babies. Most of the studies are done on Pre term babies. Nataraj et al studied on preterm babies showed decreased prevalence of Vitamin D with 800IU compared to 400IU. They had reported a small risk of Vitamin D toxicity with 800IU. But in our study we did not had any case of Vitamin D toxicity levels. Also we had comparable improvement in Vitamin D levels in both the groups

As with any study we also had few limitations in Our study like Short duration (only 3 months), Limited number of patients, Sun Exposure not accounted and Dietary intake of Breast feeding mother not taken

CONCLUSION

In Small for Gestation babies with significant deficiency, daily oral supplementation of 400 IU of Vitamin D seems adequate when compared to 800 IU upto 3 months. However long term study with larger sample may demonstrate the sufficient dose or duration of Vitamin D requirement

Acknowledgements: The authors would like to sincerely than all the parents of the babies participated in this study for co-operation and their help

Contributions: Conceptualized the study SMA,Finalized the methodology SMA&UF, Collected the data and drafted .JN,Planned and conducted statistical analysis . JN , Critically reviewed the article for intellectual content JA,All authors approved the final paper. SMA shall stand as the guarantor for this paper.

Conflicts of Intrest : None

Compliance with Ethical standards

Conflict of interest : None

Source of funding: None

REFERENCES:

1. Holick MF, MacLaughlin JA, Doppelt SH. "Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator. *Science*". 211(1981):590–593.
2. Kamao M, Tsugawa N, Suhara Y, Wada A, Mori T, Murata K, et al. "Quantification of fat-soluble vitamins in human breast milk by liquid chromatography-tandem mass spectrometry". *J Chromatogr B Analyt Technol Biomed Life Sci*. 859(2007):192–200.
3. Specker BL." Do North American women need supplemental vitamin D during pregnancy or lactation"?. *Am J Clin Nutr*. 59(1994):48-49.
4. Wagner C. "Rickets: emerging from obscurity". *Am Fam Physician*. 74(2006):561–562.
5. Ward LM, Gaboury I, Ladhani M, Zlotkin S."Vitamin D-deficiency rickets among children in Canada". *CMAJ*. 177(2007:161–166.
6. Kreiter SR, Schwartz RP, Kirkman HN, Charlton PA, Calikoglu AS, Davenport ML." Nutritional rickets in African American breast-fed infants". *J Pediatr*. 137(2000):153–157.
7. Girish M, Subramaniam G. "Rickets in exclusively breast fed babies". *Indian J Pediatr*. 75(2008):641–643.
8. Balasubramanian S, Shivbalan S, Kumar PS." Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. *Indian Pediatr"*. 43(2006):247–51] .
9. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. "High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India".*Am J Clin Nutr*. 81(2005):1060–1064.
10. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. "Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi". *Am J Clin Nutr*. 72(2000):472–475.
11. Bhalala U, Desai M, Parekh P, Mokal R, Chheda B. "Subclinical hypovitaminosis D among exclusively breastfed young infants". *Indian Pediatr*. 44(2007):897–901.
12. Seth A, Marwaha RK, Singla B, Aneja S, Mehrotra P, Sastry A, et al. "Vitamin D nutritional status of exclusively breast fed infants and their mothers". *J Pediatr Endocrinol Metab*. 22(2009):241–246.
13. Zeghoud F, Ben-Mekhbi H, Djeghri N, Garabédian M." Vitamin D prophylaxis during infancy: comparison of the long-term effects of three intermittent doses (15, 5, or 2.5 mg) on 25-hydroxyvitamin D concentrations". *Am J Clin Nutr*. 60(1994):393–396.
14. Pludowski P, Socha P, Karczmarewicz E, et al. "Vitamin D supplementation and status in infants: a prospective cohort observational study". *J Pediatr Gastroenterol Nutr*. 53(2011):93–99.
15. Mimouni FB, Shamir R. "Vitamin D requirements in the first year of life". *Curr Opin Clin Nutr Metab Care.* 12(3)(2009):287–292.
16. Wagner CL, Greer FR." American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents". Pediatrics. 122(2008): 1142–1152.
17. Agostoni C, Buonocore G, Carnielli VP, et al. "ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition". *J Pediatr Gastroenterol Nutr"*. 50(2010):85–91
18. "Guidelines on optimal feeding of low birth weight infants in low-and middle-income countries". Geneva, Switzerland: World Health Organization; 2011.Available at www.who.int/maternal_child_adolescent/documents/infant_feeding_low_ bw/en/index.html. Accessed October 25.
19. Mintoo Tergestina, Arun Jose, Santhanam Sridhar et al. "Vitamin D Status and Adequacy of Standard Supplementation in Preterm Neonates from South India". *JPGN* 58(2014):661-665.
20. Norman AW."A Vitamin D nutritional cornucopia: New insight concerning the serum 25-hydroxyvitamin D status of the US population" .*Am J Clin Nutr*, 88(2008):1455-1456.
21. Parker-Pope T. "The miracle of vitamin D : sound science orhype?" NY Times 2010: Feb.

22. Narendra Rathi, Akanksha Rathi. "Vitamin D and child health in the 21st century. Indian Pediatrics".48(2011): 619-625.
23. Bhalala U, Desai M, Parekh P, Mokal R, Chheda B. "Subclinical hypovitaminosis D among exclusively breastfed young infants. Indian Pediatr". Dec;44(2007):897-901.
24. Tergestina M, Jose A, Sridhar S, Job V, Rebekah G, Kuruvilla KA, Thomas N. "Vitamin D status and adequacy of standard supplementation in preterm neonates from South India". *J Pediatr Gastroenterol Nutr*. 2014 May 58(2014):661-665.
25. Zecca E, Romagnoli C, Alecci MC, Marchili R, Micanti M. "Prevention of hypocalcemia in low-birth-weight newborn infants: a comparative clinical study on the efficacy of ergocalciferol (Vit. D2) and calcifediol (Vit. 25(OH)D3*)". Minerva Pediatr*. 5(1990):185-188.
26. CK Natarajan, M. Jeeva Sankar, RAgarwal et al. "Trial of Daily Vitamin D Supplementation in Preterm Infants". *Pediatrics* ,133 (2014): e628-e634.
27. Ritu G and Ajay Gupta. "Vitamin D Deficiency in India: Prevalence, Causalities and Interventions". *Nutrients* 6(2014):729-775;

Address for correspondence: Prof S.Manazir Ali,
Neonatal section of ,Department of Pediatrics, JNMC, AMU, Aligarh, UP
Mobile No:+91-9837142555, E mail :manazir1958@yahoo.com

How to cite this article:S.Manazir Ali, "Vitamin D levels of the term Small for date newborns at birth and at 3 month of age after vitamin D supplementation with 2 different doses 400IU v/s 800IU- A Randomized control tria:Research Article."Vitamins and minerals 9(3)(2020):1-11.