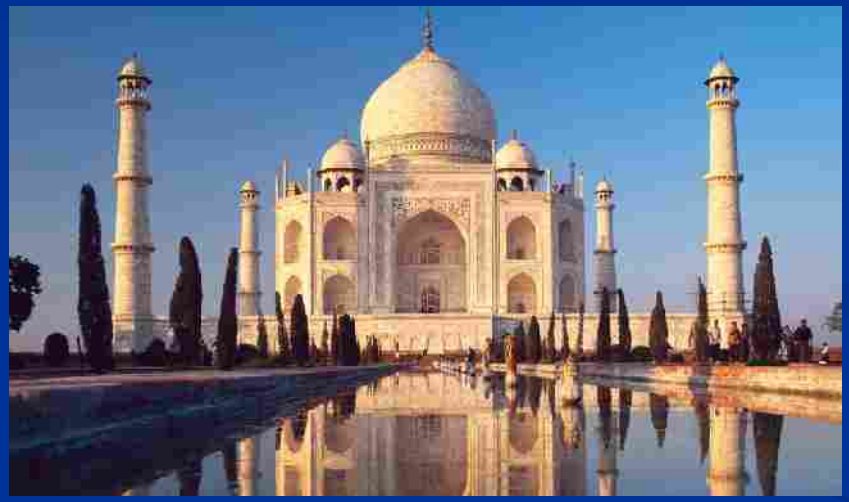
Vitamin D Deficiency in Indian Mothers, Infants and Adolescent Girls



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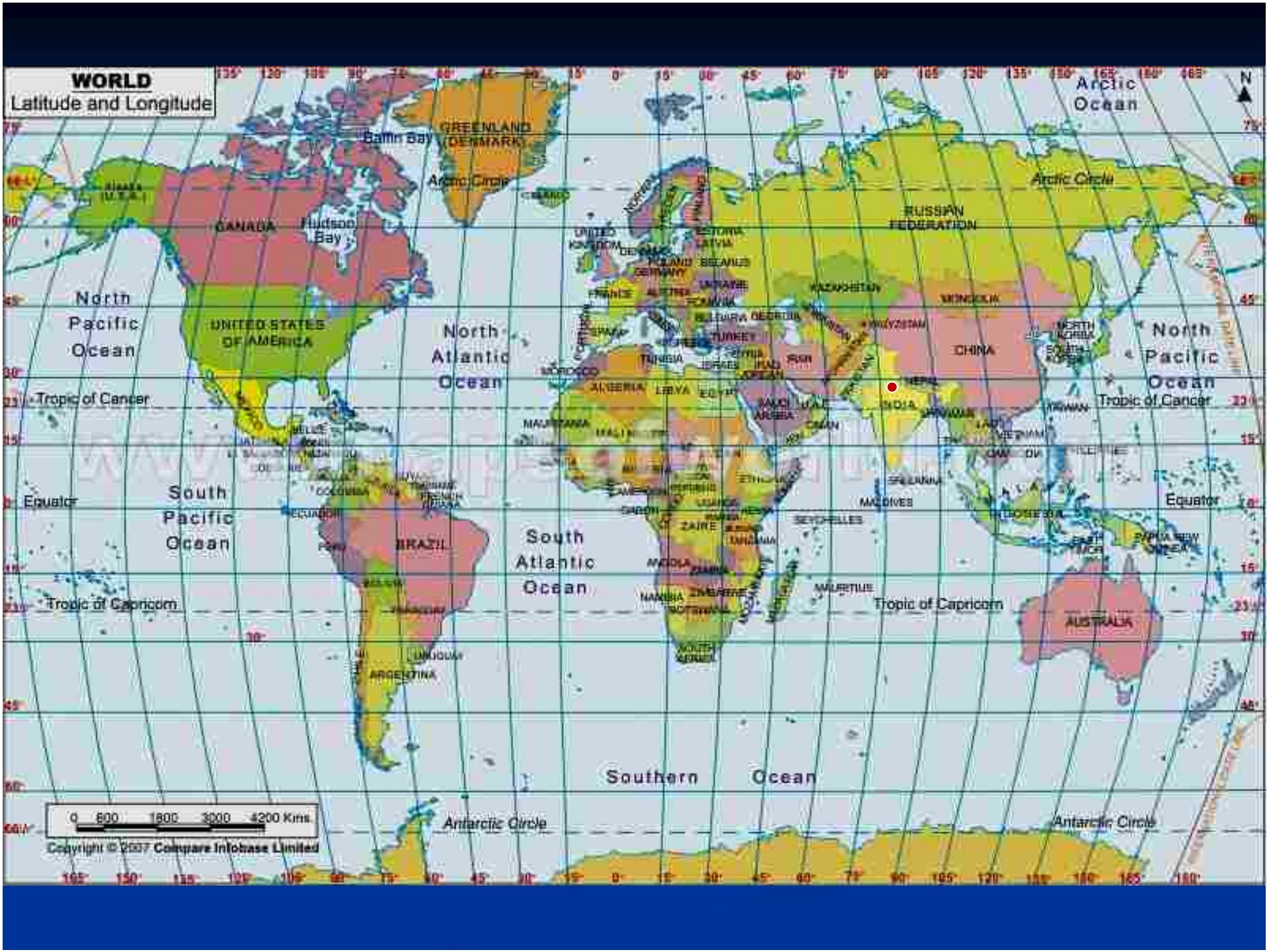
All India Institute of Medical Sciences, New Delhi

Overview of presentation

- Clinical picture of Vitamin D deficiency in Indian infants
- Studies on Vitamin D status, seasonal trends and determinants in
  - Lactating mothers and infants
  - Pregnant women & adolescent girls
- Way forward: Vitamin D supplementation


WORLD
Latitude and Longitude
Arctic Ocean
Baffin Bay
GREENLAND (DENMARK)
Arctic Circle
CANADA
Hudson Bay
RUSSIAN FEDERATION
North Pacific Ocean
UNITED STATES OF AMERICA
North Atlantic Ocean
CHINA
Tropic of Cancer
INDIA
Equator
South Pacific Ocean
BRAZIL
South Atlantic Ocean
Tropic of Capricorn
AUSTRALIA
Southern Ocean
Antarctic Circle
0 600 1800 3000 4200 Kms.
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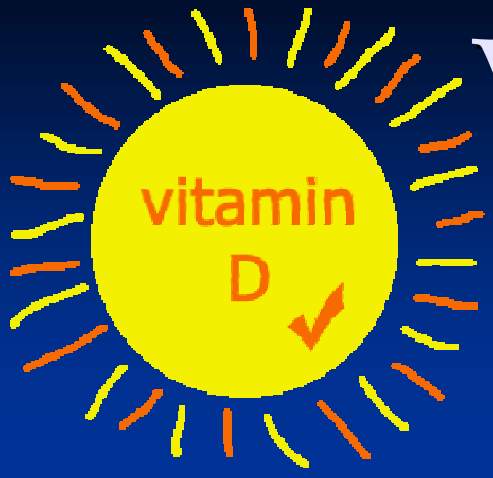


Vitamin D deficiency in Sunny India

Despite abundant sunshine, vitamin D deficiency has been recognized to be highly prevalent in India from Delhi (28°N) to Tirupathi (13°N)

MANIFESTATIONS OF VITAMIN D DEFICIENCY IN INFANTS

Rickets

Hypocalcemic Seizures

- Hypocalcemia: commonest cause of seizures in infants in many Delhi hospitals.
- 60 consecutive infants (15d- 6 mo) presenting with hypocalcemic seizures, mothers and controls recruited.

Parameter	Mothers			Infants		
	Control	Study	*P* value	Control	Study	*P* value
Serum calcium (mg/dL)	9.83±0.67	9.57±0.48	0.014	9.79±0.78	7.11±0.46	0.0001
Serum ionized calcium (mg/dL)	4.70±0.27	4.42±0.34	0.0001	4.54±0.28	3.30±0.26	0.0001
Serum ionized phosphorus (mg/dL)	3.84±0.73	4.16±0.89	0.087	4.37±0.83	3.33±1.35	0.005
Alkaline phosphatase (IU/L)	310.48±102.77	654.83±41.41	0.0001	557.23±167.41	1738.45±499.24	0.0001
25 OH vitamin D (ng/mL)	9.06±4.78	6.54±5.32	0.007	9.03 ± 4.63	4.92±4.62	0.0001
Serum parathormone (pg/mL)	64.36±56.16	60.55±37.57	0.56	69.10 ± 72.43	132.72±91.65	0.0001

Mehrotra, et al. KSC Hospital, N. Delhi Ind Pediatr 2010, 47: 581-4

Dilated Cardiomyopathy

- Retrospective case review from referral Pediatric Cardiac Centre, Delhi
- 15/ 94 cases of DCMP were attributed to hypocalcemia with high ALP in all, sec HPT in 14/15, VDD in 80%
- Age: median 2 mo (1.5 to 5)
- Wide open AF in all
- Convulsions in 7/15

Investigations	Lab findings Median (range)
Calcium	
Total (mg/dL)	5.4 (5-8.6)
Ionized (mmol/L)	0.5 (0.3-0.7)
Magnesium (mg/dL)	1.8(1.3-2.1)
Phosphorus (mmol/L)	1.4 (1.1-7)
Alkaline phosphatase (U/L)	2400 (1200-3240)
Vitamin D level (nmol/L)	30 (12.5- 62.5)
Parathyroid hormone (pg/mL)	404 (9-809)
Chest X-ray (CT ratio %)	65 (60-78)
ECG: QTc (s)	0.52 (0.51-0.58)
LVEF (%)	20 (15-30)

Tomar, et al, Ind Pediatr 2010; 47: 781-4

Prevalence of Vitamin D Deficiency in Indian Mothers and Breastfed Infants

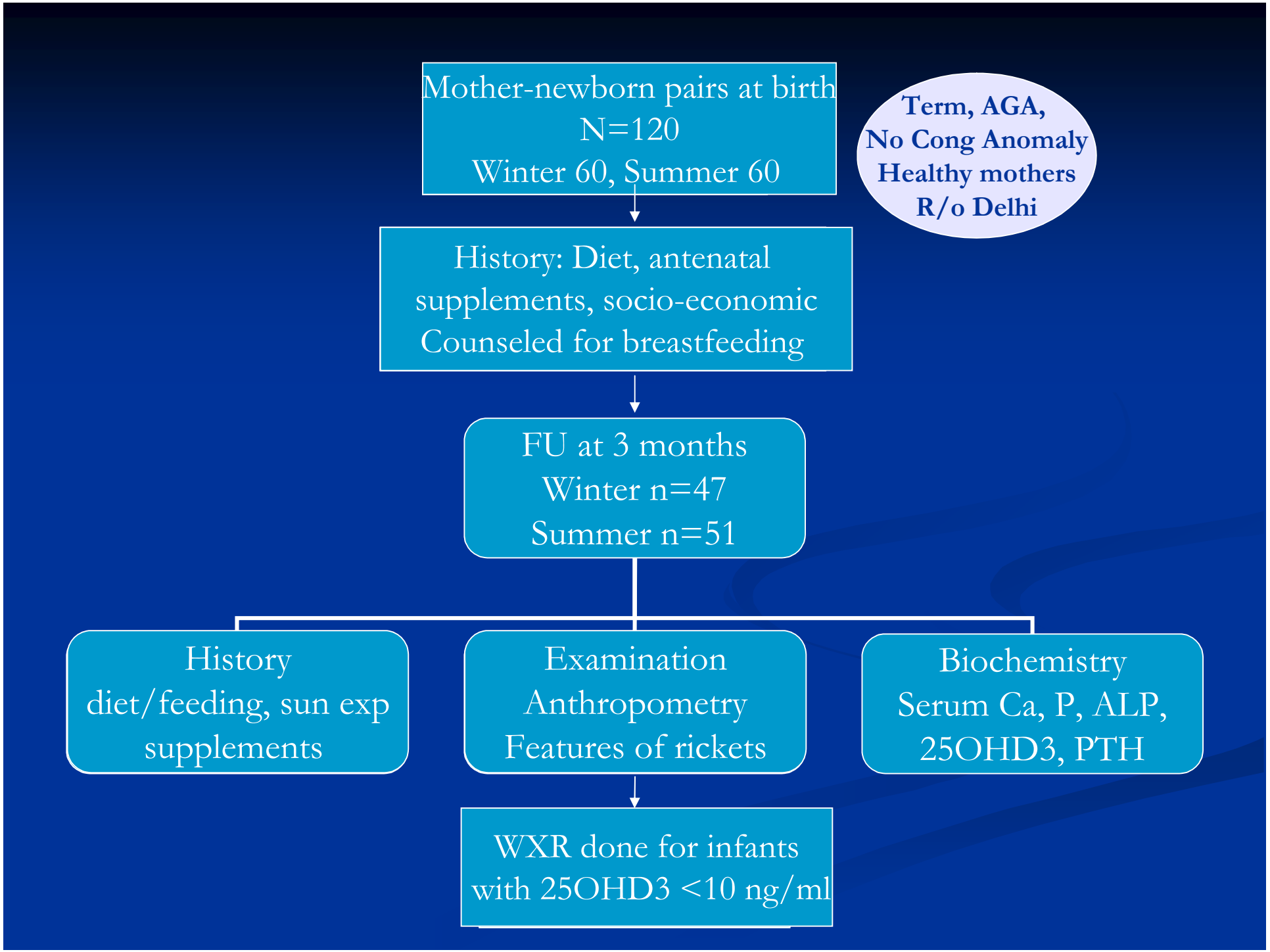
Vandana Jain, Nandita Gupta, Mani Kalaivani, Ramesh Agarwal, Aditi Sinha, Anurag Jain

Funding: AIIMS Research Grant 2006-8

Jain V, et al. Indian J Med Res 2011; 133: 267-73

Objectives

- Primary: Prevalence of Vitamin D deficiency among
  - healthy breastfed term infants at 3 months
  - their mothers
- Secondary
  - Seasonal variation
  - Determinants of vitamin D levels
  - Prevalence of radiological rickets in infants with 250HD < 25 nmol/l


Mother-newborn pairs at birth
N=120
Winter 60, Summer 60
Term, AGA,
No Cong Anomaly
Healthy mothers
R/o Delhi
History: Diet, antenatal supplements, socio-economic
Counseled for breastfeeding
FU at 3 months
Winter n=47
Summer n=51
History
diet/feeding, sun exp
supplements
Examination
Anthropometry
Features of rickets
Biochemistry
Serum Ca, P, ALP,
25OHD3, PTH
WXR done for infants
with 25OHD3 <10 ng/ml

Techniques and Definitions

25OHD: RIA, PTH: ICMA, Ca/P/ALP: Spectrophotometry

- Vitamin D[1]:
  - Deficiency: 25OHD3 <15 ng/mL (< 37.5 nmol/L)
  - Sev vitamin D def: 25OHD3 <5 ng/ml (< 12.5 nmol/L)
  - Insufficiency: 15- 20 ng/ml (37.5- 50 nmol/L)
- Elevated PTH[2]: > 46 pg/ml
- Hypocalcemia[3]: < 9 mg/dl for infants, < 8.6 mg/dl for mothers
- High ALP[3]: >420 U/l for infants and 120 U/l for mothers

1. Misra M, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics 2008; 122 : 398-417.*
2. Souberbielle JC, et al. The use in clinical practice of PTH normative values established in vitamin D-sufficient subjects. *J Clin Endocrinol Metab 2003; 88 : 3501-4.*
3. Nechyba C. Blood chemistries and body fluids. *The Harriet Lane handbook, 16th ed*

Baseline variables of infants
n=98, M: 57, F:41

Variable	Mean ± sd/ n (%)
Birth Weight (g)	2971 ± 340
Gestational age (wk)	38.3 ± 1.0
Age at sampling (wk)	13.6 ± 2.2
Exclusive breastfeeding	69 (70.6%)
Multivitamin supplement intake	34 (34.7%)
Sun exposure (recall-based)	
duration (min/d)	10 (0-120)
score	4.8 (0-12)

Anthropometry of infants at 3 months

Anthropometric parameter	Study subjects	50th centile WHO
Weight (kg)		
boys	6.2 ± 0.7	6.1
girls	5.7 ± 0.8	6.0
Length (cm)		
boys	61.8 ± 2.7	61
girls	60.8± 2.8	60
Head circum (cm)		
boys	40.5 ± 1.2	40.5
girls	39.6 ± 1.3	39.5

No growth lag/ malnutrition

Baseline variables of mothers n=98

Variable	Summary statistic
BMI	23.1± 3.3
Calcium-vit D intake	
pregnancy	96 (98%)
lactation	81 (83%)
Milk intake	
<500 ml	67 (74.4%)
>500 ml	23 (25.5%)
sunlight exposure (min)	15 (0-150)
Vegetarian diet	54 (55%)

Biochemical Parameters

Serum level	Infants	Mothers
Calcium (mg/dl)*	10.0 ± 0.8	9.1± 0.7
Phosphate (mg/dl) *	6.1 ± 0.7	4.1 ± 0.8
ALP (U/L)*	721.1± 313.4	227.0± 74.0
25OH D3 (ng/ml)* (nmol/L)	11.2 ± 8.1 28± 20.3	9.9 ± 6.1 24.8 ± 15.3
PTH (pg/ml)* #	67.2 ± 62.9 42.5 (29.9- 83.6)	60.7 ± 38.4 49 (37.9-74.9)

* mean, sd # median (interquartile range)

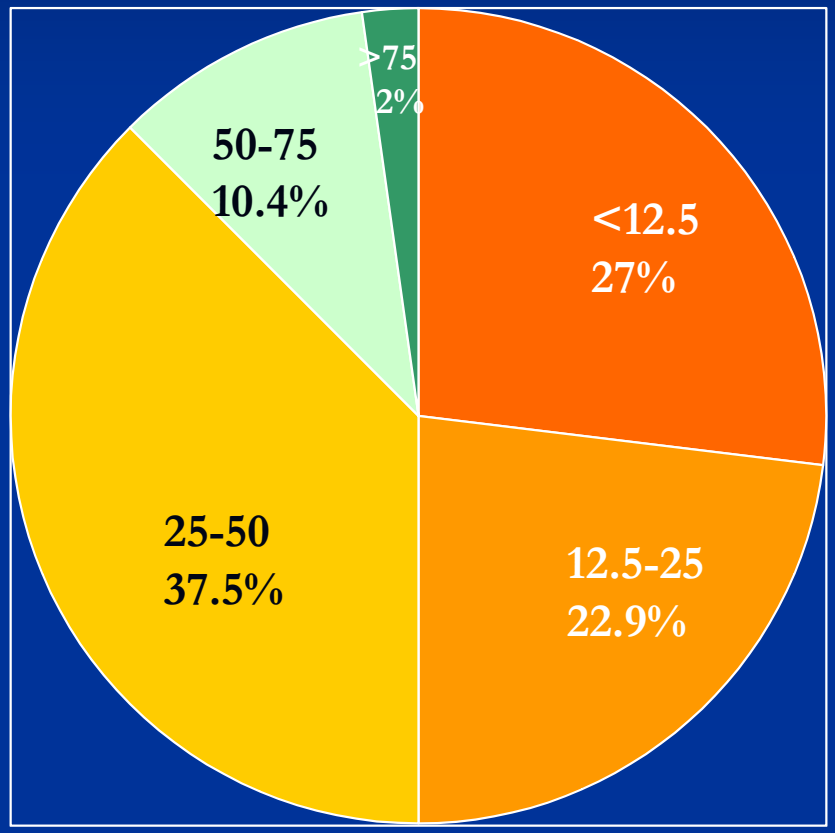
Prevalence of vitamin D deficiency and its biochemical markers in infants and mothers

Parameter	Infants n (%)	Mothers n (%)
Vitamin D deficiency	64 (66.7)	77 (81.1)
Vitamin D insufficiency	19 (19.8)	11 (11.6)
Severe vitamin D deficiency	26 (27.1)	22 (23.2)
Hypocalcemia	7 (7.1)	23 (24.2)
Raised ALP	89 (91.8)	92 (96.8)
Hyperparathyroidism	47 (48.5)	52 (53.7)

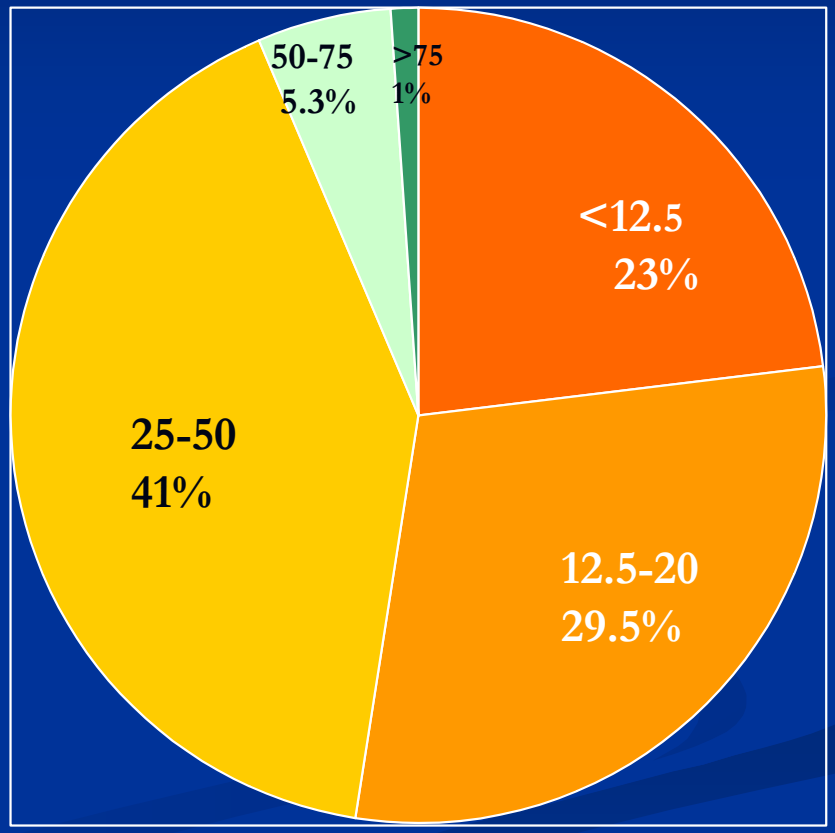
25OHD < 20 ng/ml (< 50 nmol/L) : Infants: 86.5%(78.0, 92.6)
Mothers: 92.6% (85.4, 97.0)

Frequency Distribution of 25OHD

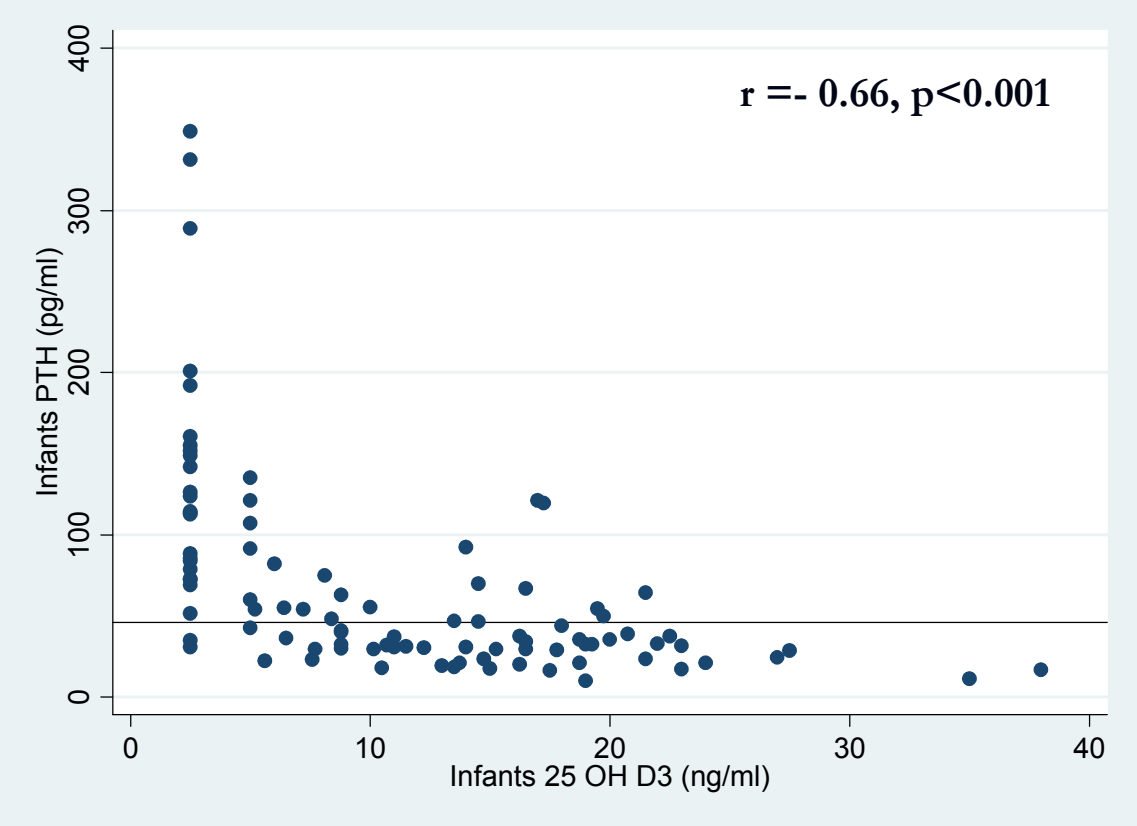
Infants



Mothers

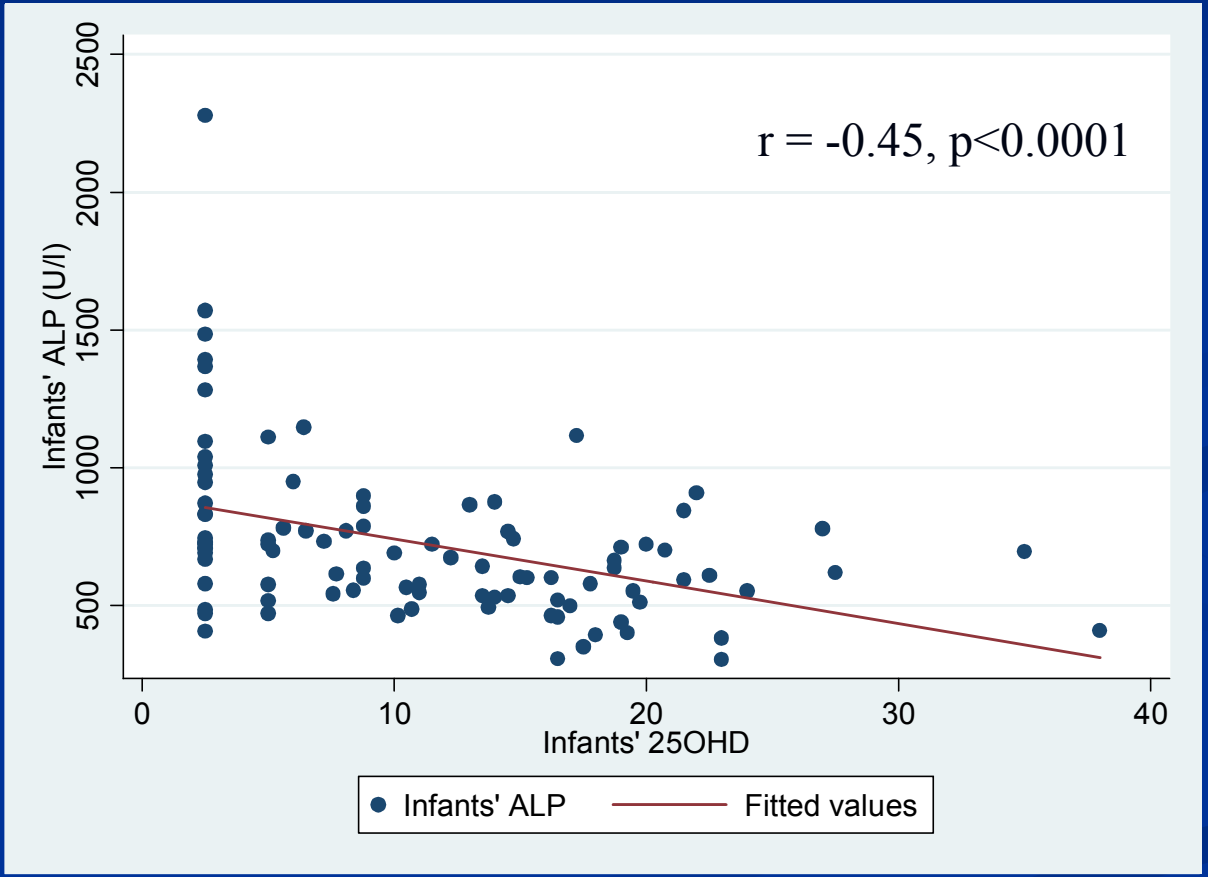


Relation between Infants' PTH and 25OHD levels

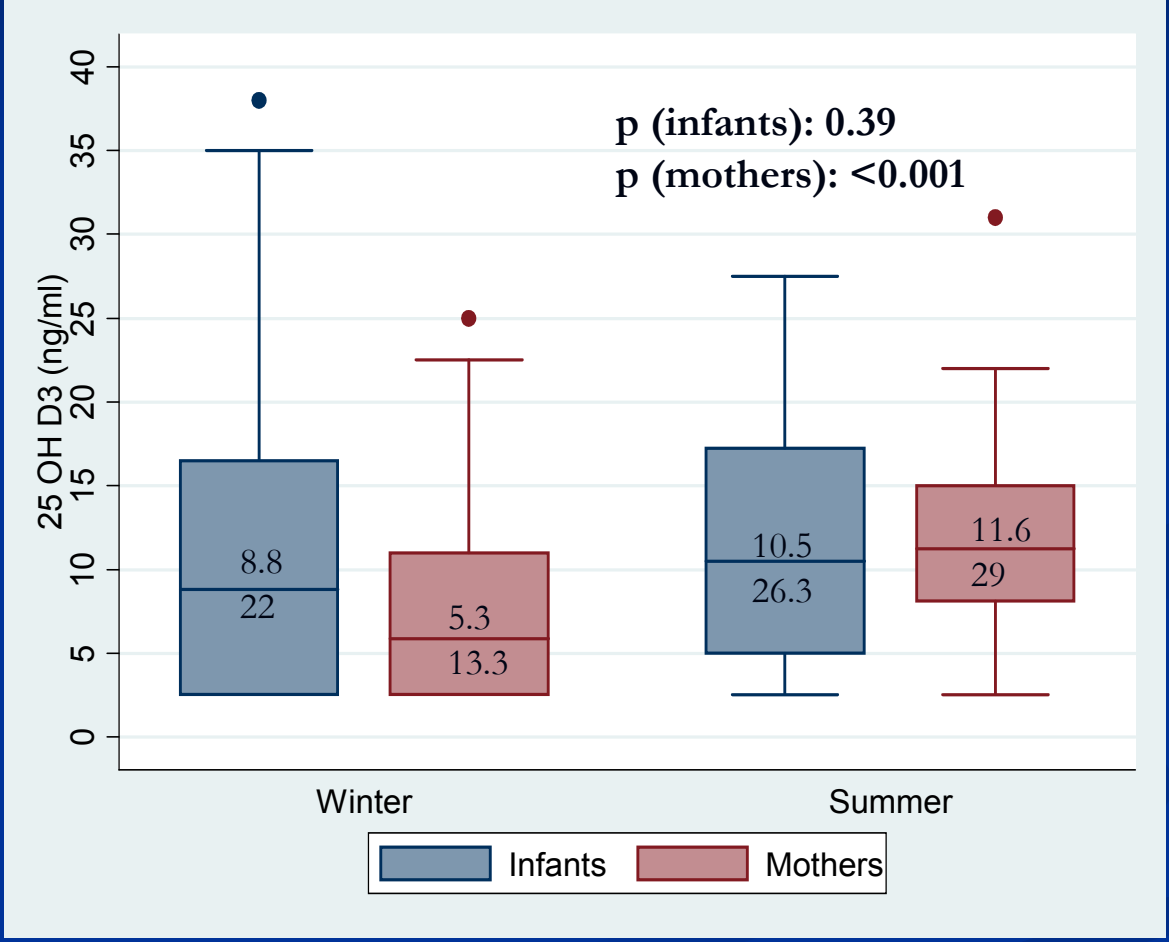


Among infants and mothers with VDD (< 15ng/ml, < 37.5 nmol/l), HPT in 63 & 57%
Amongst those with severe VDD (< 5ng/ml, < 12 nmol/l), HPT in 90 and 73%

Relation between Infants' ALP and 25OHD levels



Effect of season on 25OHD



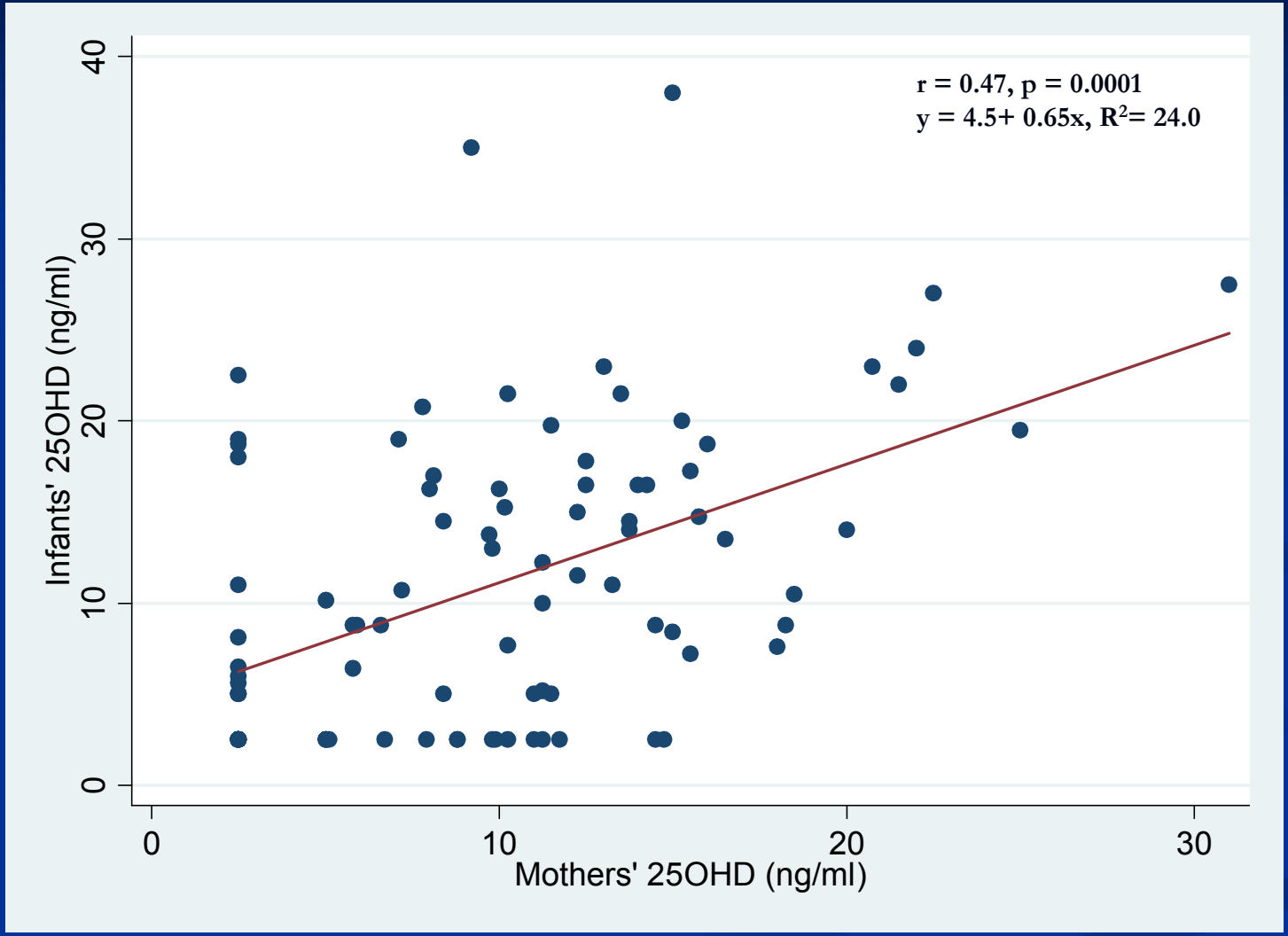
Wrist X-Ray for rickets in infants with 25OHD < 25 nmol/l

- Early changes: 10/33

Predictors of infants' 25OHD by linear regression analysis

Variable	Univariate			Multivariate	
	β (SE)	p-value	R^2	β (SE)	p-value
Vitamin supplement	4.80 (1.65)	0.005	8.2	3.46 (1.52)	0.025
Sunlight exposure	0.006 (0.002)	0.009	7.5	0.007(0.002)	0.001
Mother's 25 OHD (ng/ml)	0.65 (0.12)	0.0001	24.0	0.61 (0.117)	0.0001

Relation between infants' 25OHD levels and mothers' 25OHD levels



Why the high prevalence?

- Low cutaneous synthesis owing to higher pigmentation
- Greater coverage of body and lesser participation in outdoor activities, in particular among girls, starting from adolescence
- Decline of the traditional custom of giving infants an oil massage in the sunlight for 15-30 min before bathing

Why the high prevalence?

- No food items (except infant formula) fortified
- No policy of routine vitamin D supplementation in pregnant/lactating women and infants
- Indian diet, low in calcium and high in phytates, may contribute by causing secondary HPT, increased conversion of 25OHD to polar metabolites and 24, 25 dihydroxy D3

Vitamin D deficiency in rural Indian women & adolescent girls

Sahu M, et al. Clinical Endocrinology (2009),**70,** 680–4

Pregnant women (*n* = 139)

	Pregnant women
Age (years)	26·7 ± 4·1
Summer sun exposure (h/day × % BSA)	35·4 ± 15·9
Winter sun exposure (h/day × % BSA)	26·8 ± 8·1
Serum 25OHD (nmol/l)	37·8 ± 19·8
Vitamin D deficiency (< 50 nmol/l)	103 (74%)

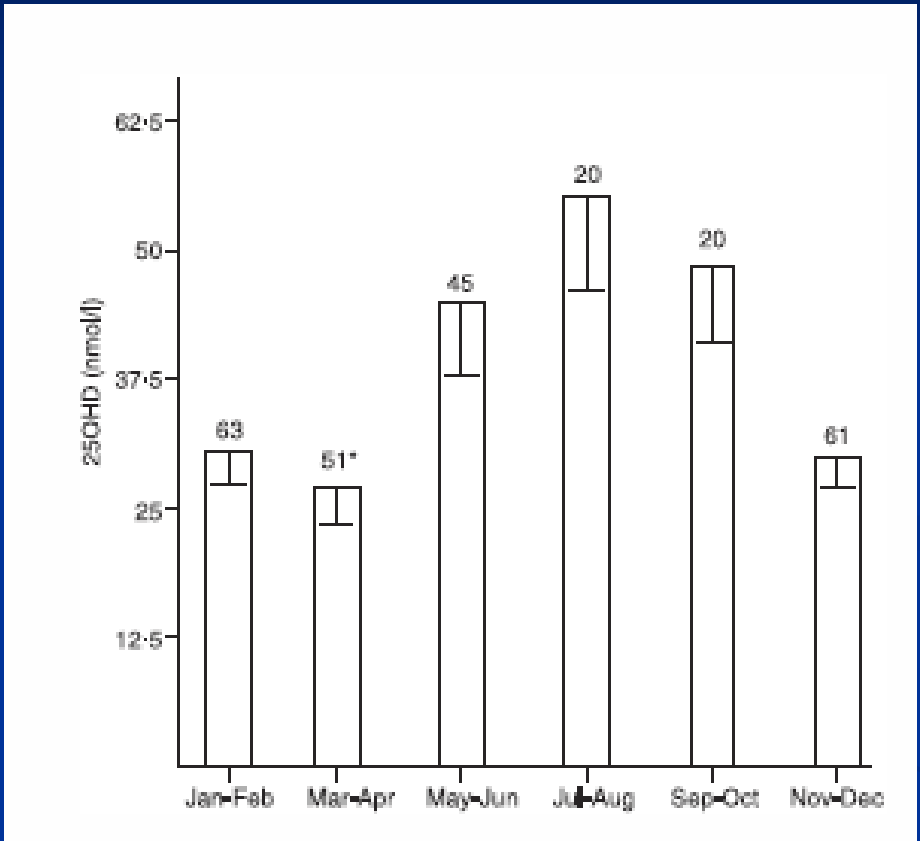
Adolescent girls (n=121)

Comparison with brothers

Serum 25OHD (nmol/l)	33·3 ± 16·0
Vitamin D deficiency	107 (88%)

	Boys (*n = 34*)	*Girls (n = 28)*
Age (years)	14·0 ± 3·0	14·4 ± 2·7
Pubertal staging	3·0 ± 1·5	3·7 ± 1·2
Summer sun exposure (h/day × % BSA*)	49·1 ± 15·7	30·5 ± 20·7*
Calcium intake (mg/day)	384 ± 600	198 ± 159
Serum 25OHD (nmol/l)	67·5 ± 29·0	31·3 ± 13·5*
Vitamin D deficiency	9 (27%)	25 (89%*)

Seasonal Variation in 25OHD levels of adolescent girls and pregnant women (n= 260)



	Summer (May-Oct)	Winter (Nov-April)
Mean 25OHD nmol/l	: 55·5 ± 19·8	27·3 ± 12·3
Hypovitaminosis D	54%	93%

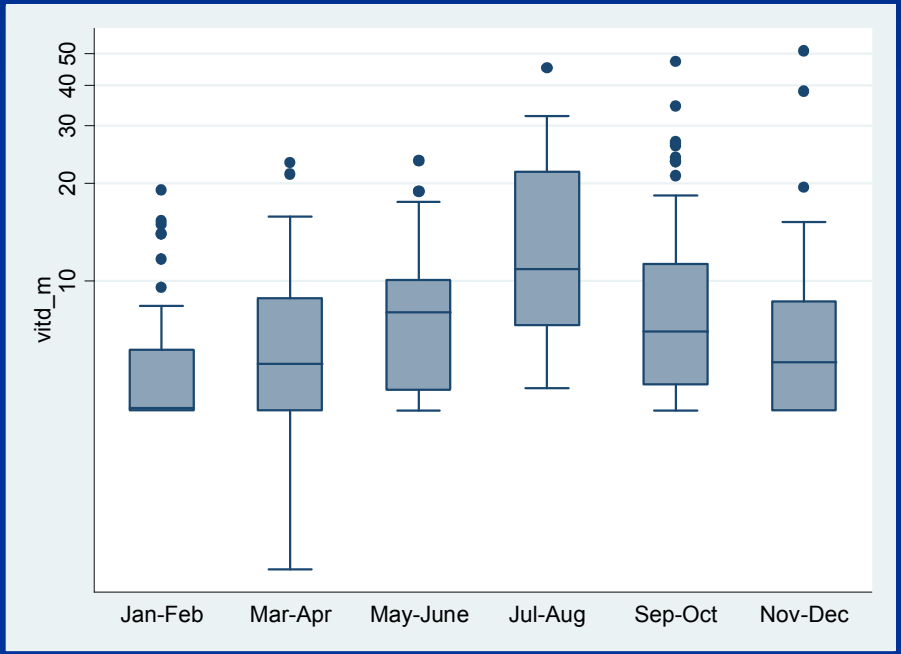
Vitamin D status at birth in LBW infants and mothers

- Agarwal R, et al. AIIMS, N. Delhi, 2009-10
- 220 LBW (< 2500 g) Gest age <32 wk (n=11) ; 32-36 wk (n=98) and ≥37 wk (n=111)
- 126 NBW infants and their mothers enrolled

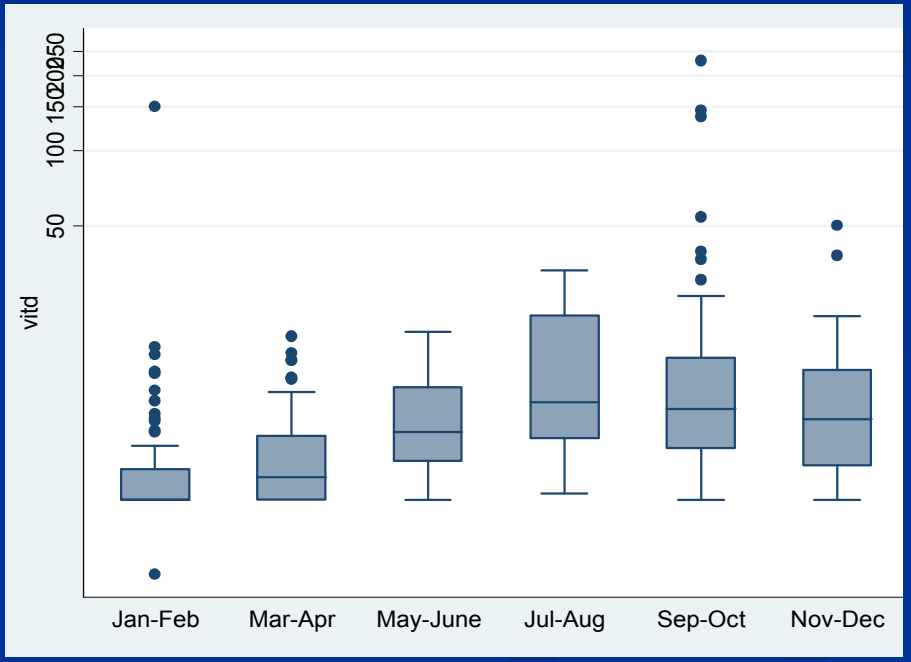
	LBW group (n= 220)		NBW group (n=126)	
	Infants	Mothers	Infants	Mothers
25OHD (nmol/L)	16.3 (10-125)	13 (10-95)	14 (10-63)	15 (10-78)
Hypovitaminosis D	93%	93.5%	95.1%	96.7%

Seasonal variation

MOTHERS



INFANTS



Other Indian Studies

Author, Site Journal, Year	Study population	Results
Marwaha, et al, Delhi Br J Nutr (2008)	Healthy School girls (6-18 y), n=404	Mean: 12.1 ± 6.7 ng/ml Prevalence of VDD (< 20 ng/ ml): 90.8%
Sachan A, Lucknow AJCN 2005	207 pregnant women 117 cord blood	25OHD <22.5 ng/ ml: 84% women Mean 14 ± 9.3 (Women) 8.4 ± 5.7 (Cord)

VITAMIN D SUPPLEMENTATION TRIALS

School girls (Delhi)

- 290 girls with mean age of 12 years supplemented with either 1 monthly or 2 monthly supervised dose of 60,000 IU cholecalciferol orally for 1 year.

	2-monthly group	1-monthly group
Prevalence of hypovitaminosis D %		
Baseline	94	88
6 m	84	68
12 mo	80	57
25OHD levels (nmol/L, mean (SD))		
Baseline	29.1 (1.5)	30.8 (1.4)
6 m	39.5 (1.2)	46.8 (1.5)
12 mo	38.3 (2.1)	49.9 (2.0)

Marwaha, et al. Ind Pediatr 2010; 47: 761-5

Pregnant women (rural N. India)

- N=139, baseline Se 25OHD: 32.3 (22.8-50.1 nmol/l)
- 3 groups:
  - A: no supplementation
  - B: 60,000 U once in 5th month
  - C: 120,000 U twice (in 5th and 7th month)

- Significant increase only in group C: 40.1 (26.9-58.4 nmol/l) at baseline vs 53.4 (41.2-88.0 nmol/l) after delivery, P<0.001
- Even in group C, only 20% achieved 25OHD> 80nmol/l

Sahu M, et al. Eur J Clin Nutr. 2009;63:1157-9

Stoss therapy: Safety and Efficacy

Jain V et al, ongoing, n=10 till now

- Monitoring Se Ca, P, ALP, 25OHD and PTH in infants who have received Inj Vit D 6 lac U i.m. single dose for treatment of rickets/ hypocalcemic seizures at 3, 6 and 12 mo for efficacy and safety

- At 3 mo, 4/ 12 had hypercalcemia (Se Ca > 10 mg/dl), 25OHD > 200 nmol/l

- By 1 year, 3/ 5 have Se 25OHD < 50 nmol/l


SLOW