

# Very High Prevalence of Severe Vitamin D Deficiency in Breastfeeding Mother-Infant Dyad in a Sunny Middle Eastern Environment

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# Randomized Controlled Trial of Vitamin D Supplementation of Lactating Women to Prevent Vitamin D Deficiency in Mothers and Their Infants: Protocol

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## Important Considerations Regarding Vitamin D Status

- When a woman is deficient in vitamin D, her developing fetus is deficient.
- Similarly, a lactating woman who is deficient in vitamin D, provides breast milk that is deficient in vitamin D--
  - therefore, unless her breastfeeding infant is supplemented, her breastfeeding infant will be deficient.

# Results of Previous Pilot Studies

- Vitamin D supplementation of mother with higher doses improved maternal vitamin D status, and in so doing, increased her milk antirachitic activity, and thus, the transfer of vitamin D to her nursing infant.
- They also showed both efficacy and effectiveness
- What needs to be shown is safety and effectiveness on a larger scale

- **Vitamin D (vitD) deficiency rickets is mostly reported worldwide among breastfed infants who lack exposure to sunshine and/or vitD supplementation.**
- **Reports of vitD status of breastfeeding (BF) infants and their mothers in high-risk populations are scarce.**

# Vitamin D Supplementation of Breastfeeding Arab Women and Infants: Qatar Study

- Objectives

- Examine the effect of high dose maternal vitamin D supplementation of 6000 IU/day alone vs current recommendation of direct maternal suppl. Of 600 IU/day plus infant suppl. Of 400 IU/day.
- Determine the effect of high dose supplementation on the vitamin D content of human milk.

- Hypothesis

- High dose (6000 IU/day) maternal supplementation alone can maintain the serum 25(OH)D levels of her infant at equivalent level to that of infant on current direct supplementation with 400 IU/day.
- Through increase in human milk content with no differences in safety measures.

# Primary Outcome Variables

1. Maternal serum 25(OH)D levels at 4 weeks , 4 months and 7 months postpartum and monthly urinary ca/cr ratios.
2. Infant serum 25(OH)D levels and serum calcium at 4 weeks, 4 and 7months postpartum.

# Methods and Study Design

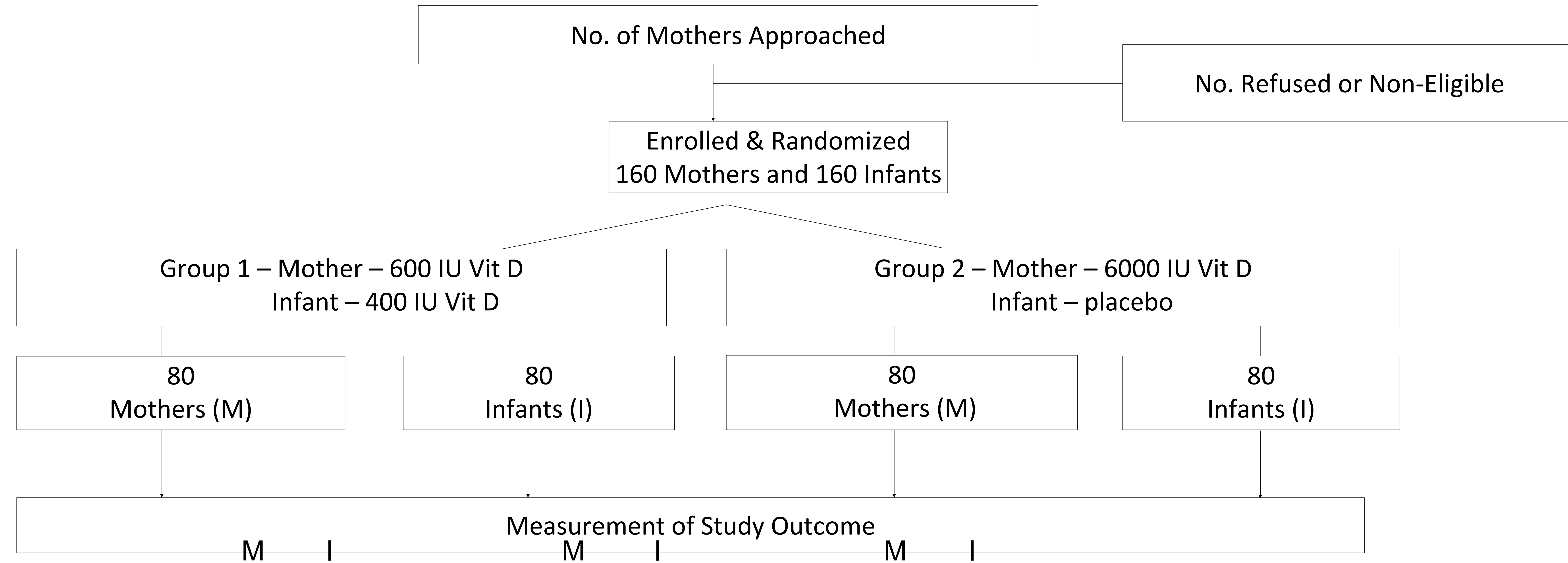
- Healthy women with singleton delivery and were eligible to participate.
- Exclusions were diabetes, hypertension and vitamin D treatment.
- Monitoring for effectiveness and safety.
  - Serum 25(OH)D, Ca, PTH at 4wks 4 and 7 m postpartum (mother and infant)
  - Maternal urine Ca/Cr ratio at monthly interval
- Adverse events recorded and reported to DSMC.



# Randomization

- Administrative secretary not involved in the study assigned randomization code generated by computer to each case.
- Only case number appears on the case report form.
- The chair of DSMMC may have access to the codes.
- The investigators and health team will be blinded to different treatments till analysis.

# Vitamin D Supplementation of Lactating Mothers to Prevent Vitamin D Deficiency in Mothers and Infants



Tests	<u>4 Weeks</u>		<u>4 Months</u>		<u>7 Months</u>	
	M	I	M	I	M	I
Serum 25(OH)D	x	x	x	x	x	x
Serum PTH	x	x	x	x	x	x
Serum Calcium	x	x	x	x	x	x
Urine Calcium*	x	-	x	-	x	-
Urine Creatinine*	x	-	x	-	x	-
Milk ARA	x	-	x	-	x	-
<u>Clinical</u>						
Weight	x	x	-	x	-	x
Height/Length	x	x	-	x	-	x
Head Circumference	-	x	-	x	-	x
Questionnaires	x	x	x	x	x	x

\*Maternal Urine Ca and Cr and pregnancy test will be measured monthly.

# Summary Slide

- Vitamin D supplementation of mother with 6000 IU/day only vs maternal 600 IU/day plus infant 400 IU/day.
- Follow up infants and mothers, complete questionnaires, samples for laboratory measurements, record adverse events, complete log enrollment and database.
- Analysis of results and preparation of reports.

- We determined vitD status at enrollment (Aug-Sept 2014) in the first 107 consecutive mothers and infants participating in a randomized controlled trial of high-dose vitD supplement to prevent vitD deficiency.
- Arab mothers who delivered at term ( $\geq 37$  wks) and planned to provide predominantly BF for at least 6 months were enrolled at 4 wks post-partum.
- Data were collected on maternal and infant vitD supplement, time spent outdoors in direct sunlight and body surface area (BSA) exposed while outdoors (Table 1: BSA calculator).
- Primary outcomes were maternal and infant serum 25(OH)D.
- Comparison was made of sun exposure, vitD supplementation, and vitD status with BF mothers studied in Cincinnati, Ohio, at similar postpartum age and season.

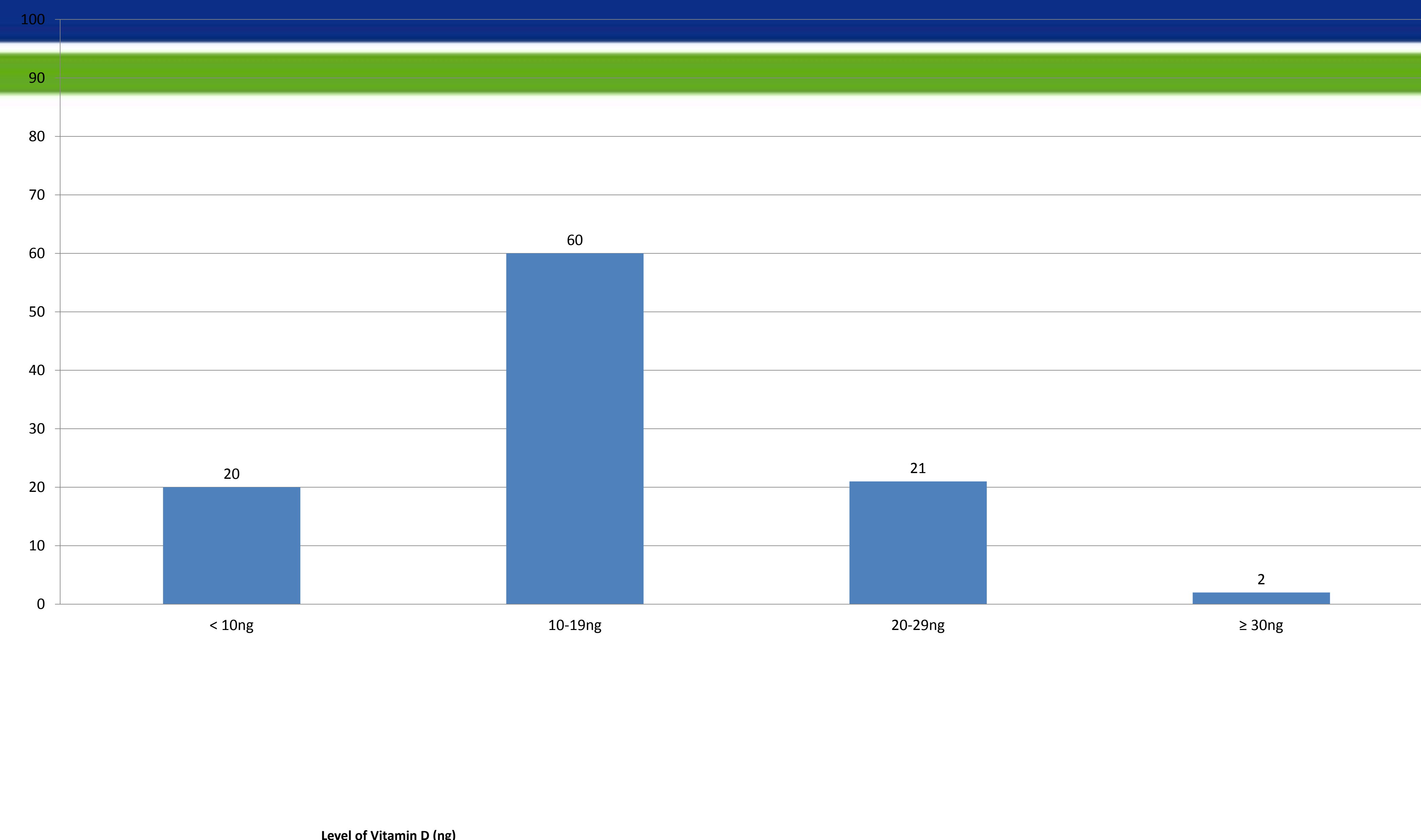
**Table 1: Calculation of percent body surface are (%BSA) exposed to sunlight<sup>a</sup>**

Usual Outdoor Daylight Attire In Past Week			%BSA assigned for	
Body part	Type of covering	Response	Mother	Infant
Head	Hat, cap, or head scarf	Yes	0	0
		No	3	12
Neck	Clothing or scarf	Yes	0	0
		No	2	2
Face	Scarf	Yes	0	0
		No	4	7
Arms	Length of sleeves	Long	0	0
		Short	6	6
		Sleeveless	14	14
Hands	Gloves	Yes	0	0
		No	5	5
Legs	Length of pants or dress	Long	0	0
		Short (below knee)	7	5
		Short (knee length)	14	10
		Short (mid-thigh)	23	16
Feet	Amount of coverage	Covered	0	0
		Barefoot or sandals	7	7

<sup>a</sup>Total %BSA exposed to sunlight calculated as the sum of %BSA associated with subject's responses for each body part.

- Serum concentrations of 25(OH)D were measured by CLIA (DiaSorin) and PTH by CLIA (Beckman Dxl).
- Vitamin D deficiency was categorized as serum 25(OH)D <50 nmol/L ( 20 ng )and severe vitD deficiency associated with osteomalacia or rickets as <30 nmol/L (10 ng.

No. of Mothers

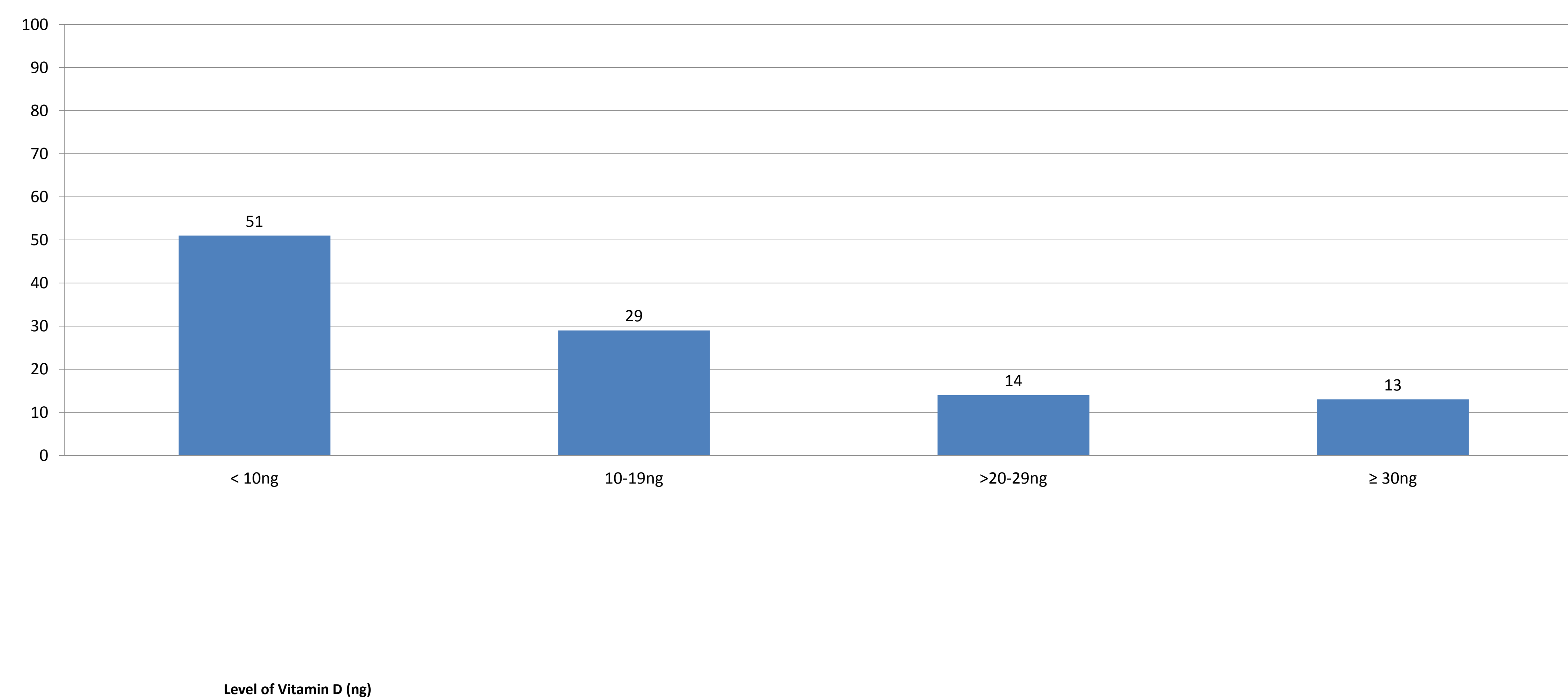


### Vitamin Level (Basic) of Mothers

< 10ng	20
10-19ng	60
> 20-29ng	21
≥ 30ng	2

Vitamin D Level of Babies during Visit 1

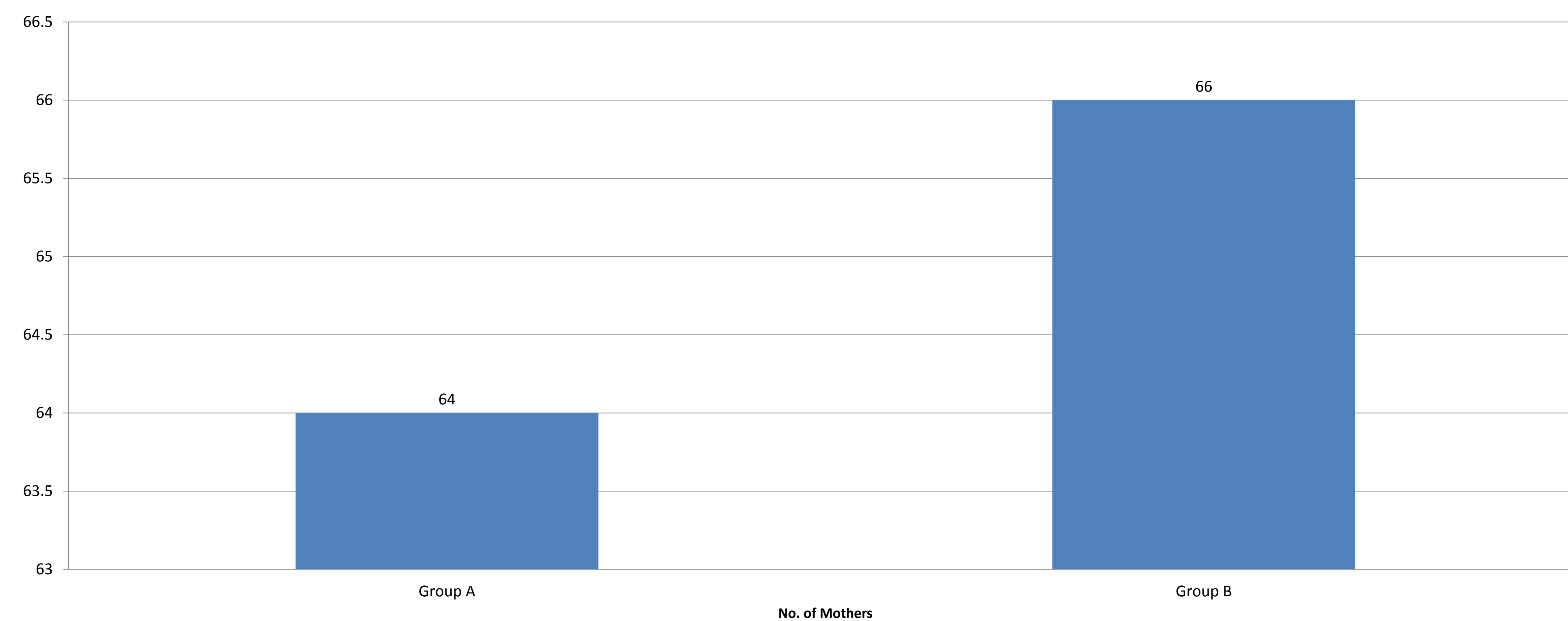
No. of Baby



### Vitamin Level (Basic) of Babies

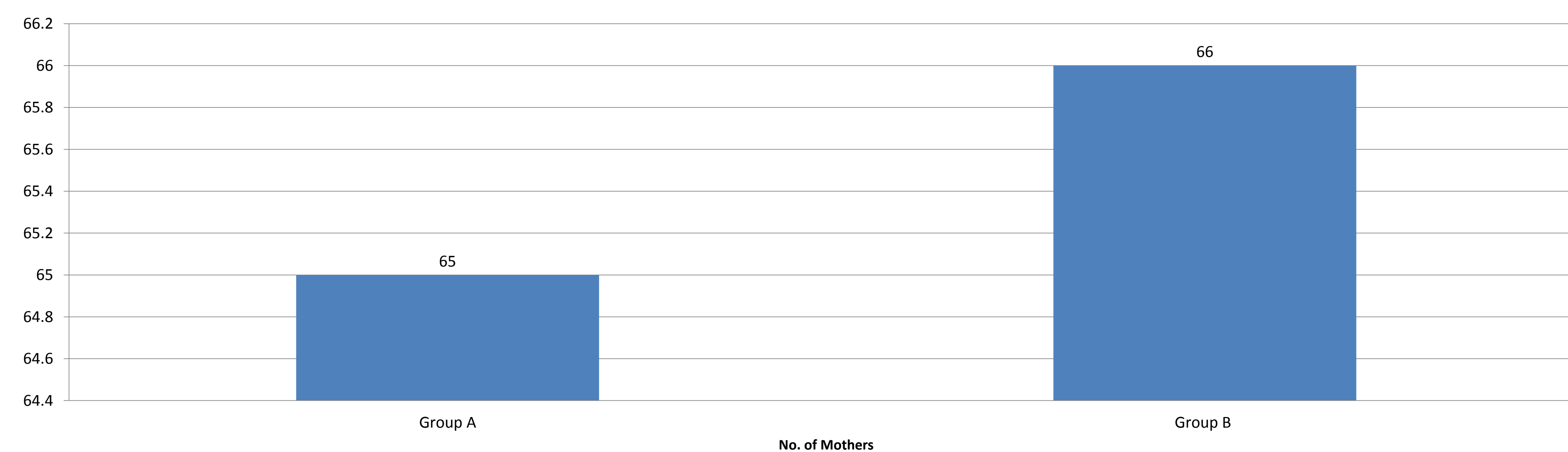
< 10ng	51
10-19ng	29
> 20-29ng	14
≥ 30ng	13

Vitamin-D level (Basic) of Mothers on Visit 1



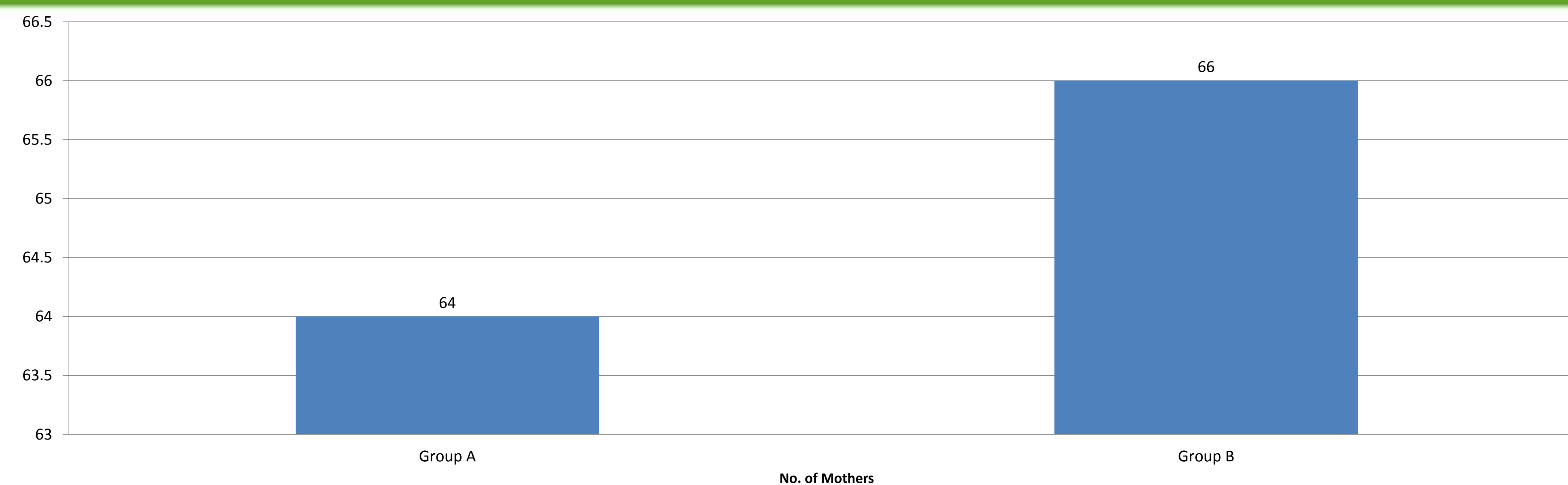
Vitamin Level (Basic) of Mothers on Visit 1	
Group A	64
Group B	66
Average Vitamin D	14

Vitamin-D level (Basic) of Babies on Visit 1



Vitamin Level (Basic) of Babies on Visit 1	
Group A	65
Group B	66
Average Vitamin D	11

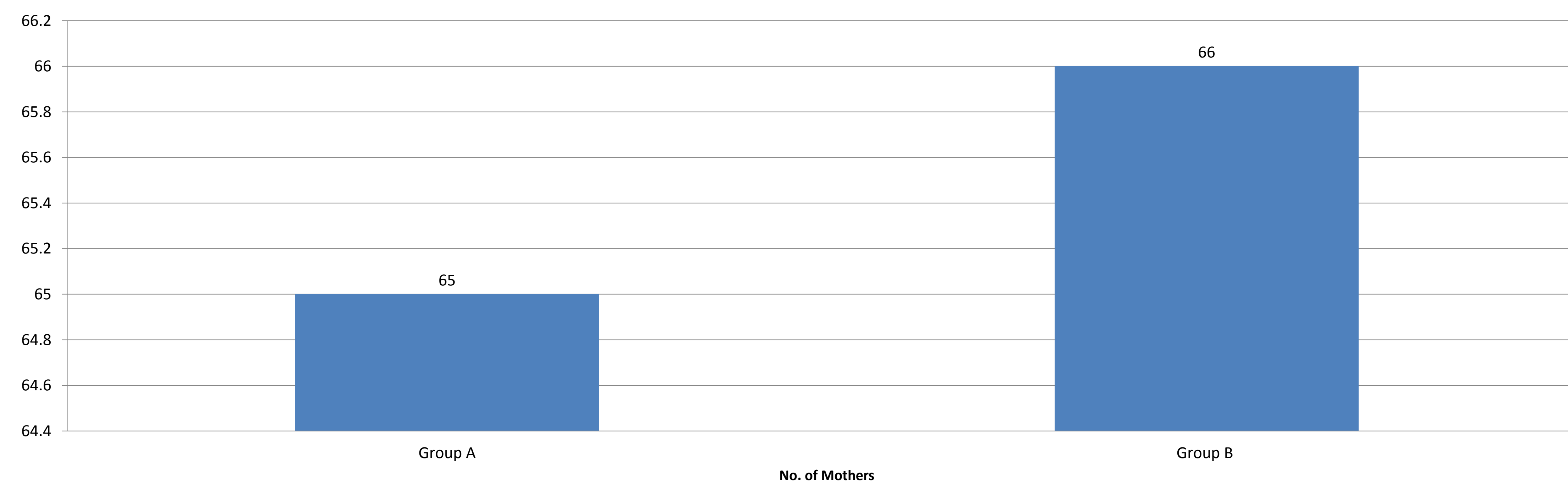
Average Vitamin-D level of Mothers on Visit 2



Ave. Vitamin D Level of Mothers on Visit 2

Group A	28
Group B	27

Average Vitamin-D level of Babies on Visit 2

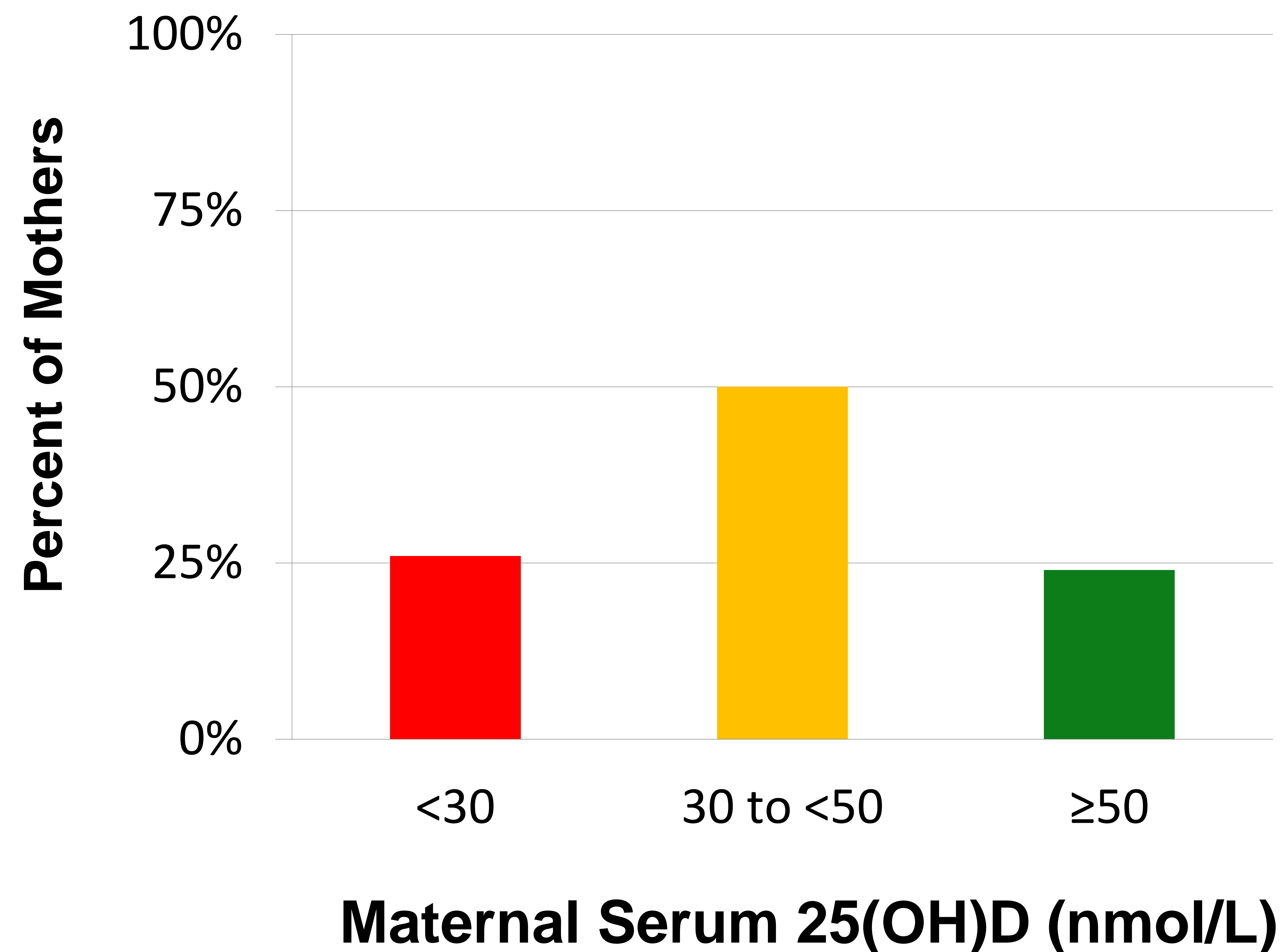


Ave. Vitamin D Level of Babies on Visit 2

Group A	31
Group B	32



Figure 1. Categories of Maternal Vitamin D Status At 4 Weeks Postpartum



## Mothers

- Mean (SD) serum 25(OH)D was 37.3 (16.3) nmol/L. Total of 76% were vitD deficient (Figure 1).
- Negative correlation between 25(OH)D and PTH was insignificant ( $r=-0.16$ ,  $p=0.21$ )

- Milk vD content was measured using LC/MS and serum 25-OH(D) concentration by CLIA (DiaSorin). Milk vD levels were categorized as: a) below assay detection ( $< 8.2$  IU/L), b) below normal range (8.2 to  $< 20$  IU/L) c) within normal range ( $\geq 20$  IU/L) (**ref 1**). Serum 25(OH)D  $< 50$ nmol/L was defined as vitamin D deficiency (**ref 2**).

# Results

- The mean (SD) maternal milk vD level was 12.6 (15.3) IU/L.
- Prevalence of maternal vitamin D deficiency was very high while maternal sun exposure was very low and diet vitamin D intake was low. (Table 2).
- 75% of the mothers have milk vD levels below assay detection at 4 weeks postpartum (Fig 1)
- Serum 25(OH)D levels were significantly lower in mothers with milk vD below assay detectable levels than those with milk vD values above detectable levels ( $z=2.8$ ,  $p=0.005$ ). (Fig2)
- Maternal Serum 25(OH)D correlated with maternal milk vD levels ( $r=0.37$ ,  $p < 0.004$ ). There were no correlations among milk vD content and maternal age, education, vD intake and sun index score.

**Table 2. Maternal Sun Exposure and Vitamin D Status in Doha and Cincinnati Study\***

Variable	Doha N=62	Cincinnati N=48
Month of study	August-September	June-August
Latitude	25°N	39°N
Average sunshine hrs/day	10	10
<b>Sun exposure behavior<sup>+</sup></b>		
% BSA exposure outdoors	9 (9, 9)	43 (34, 50)
Sun exposure hrs/wk	0 (0, 0.42)	4.3 (2.1, 8.0)
Sun index	0 (0, 3)	198 (90, 383)
<b>Vitamin D supplementation</b>		
% any supplementation	47	87
<b>Vitamin D status</b>		
Serum 25(OH)D nmol/L [mean (SD)]	37.3 (16.3)	75.3 (26.9)
% serum 25(OH)D <50 nmol/L	80	17
<sup>+</sup> values are median (IQR)		

Sun Index = sun exposure x BSA

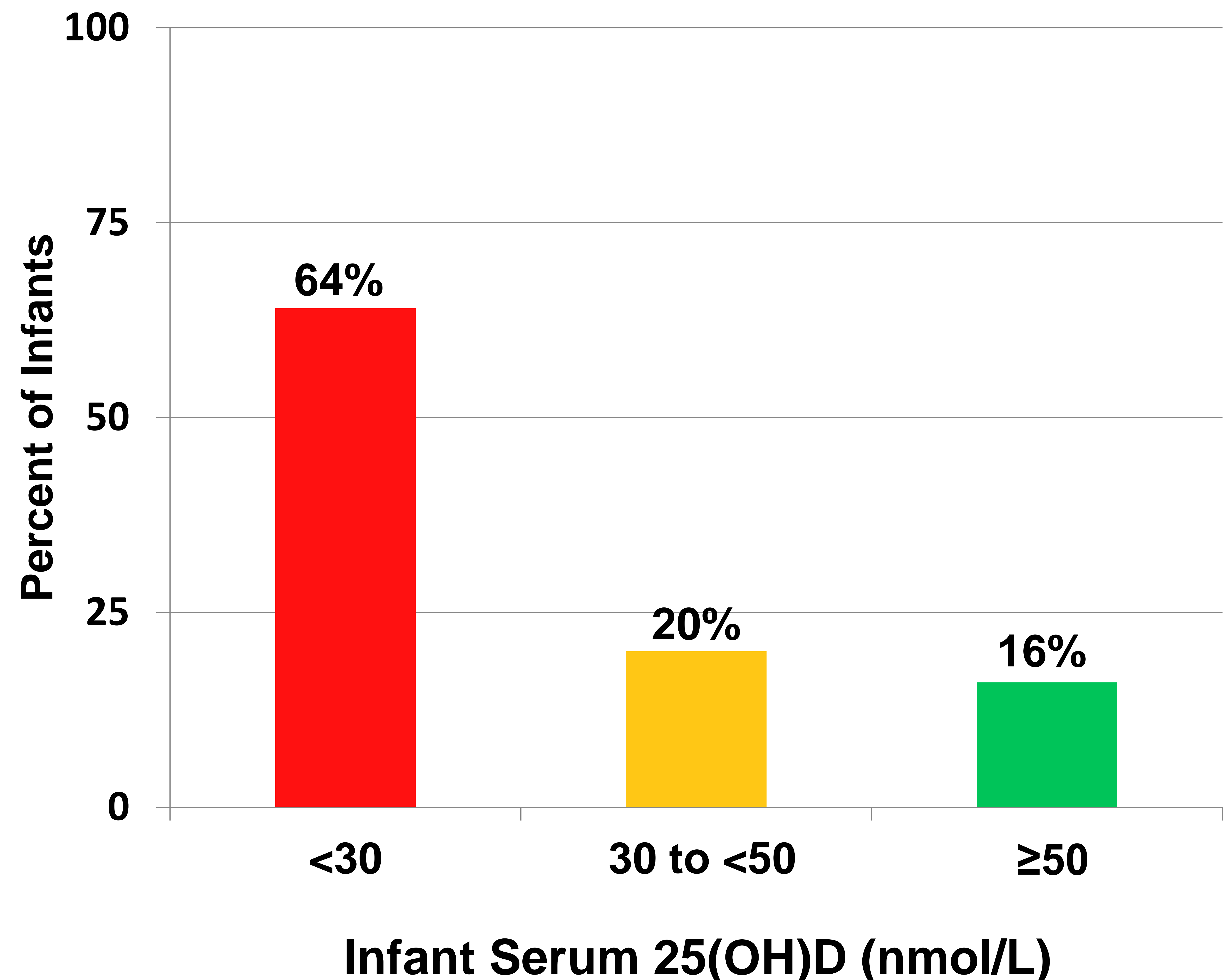
\*Dawodu A, et al. PAS 2013 Annual Meeting (Abst) E-PAS 2013:3831.

- Predictors of vitD status in BF mothers.
  - Percent BSA exposure while outdoor correlated with serum 25(OH)D concentration ( $r=0.28$ ,  $p=0.03$ ).
- Sun exposure behaviors, vitD supplementa-tion rate, and vitD status in summer season were significantly higher in mothers in Cincinnati study than in Doha (Table 2).

## Infants

- Mean (SD) serum 25(OH)D was 27.9 (8.4) nmol/L.
- Overall 84% are categorized as deficient and over 60% severely deficient (Figure 2).
- Serum 25(OH)D concentration correlated with maternal values ( $r=0.53$ ,  $p=0.0001$ ).
- Negative correlation between 25(OH)D and PTH was insignificant ( $r=-0.07$ ,  $p=0.62$ )
- None of the infants had received vitD supplement or had been exposed to sunlight.

Figure 2. Categories of Infant Vitamin D Status



- **Severe vitD deficiency is more common in infants than mothers in sunny environment.**
- **Low maternal vitD status is associated with low sun exposure and vitD intake.**
- **We speculate that low vitD status in infants is related to low status at birth aggravated by no sun exposure and vitD intake.**
- **Vitamin D supplementation of mothers and infants would help prevent deficiency.**



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