VITAMIN D REQUIREMENTS DURING PREGNANCY, LACTATION, & EARLY INFANCY: A MOVING TARGET?

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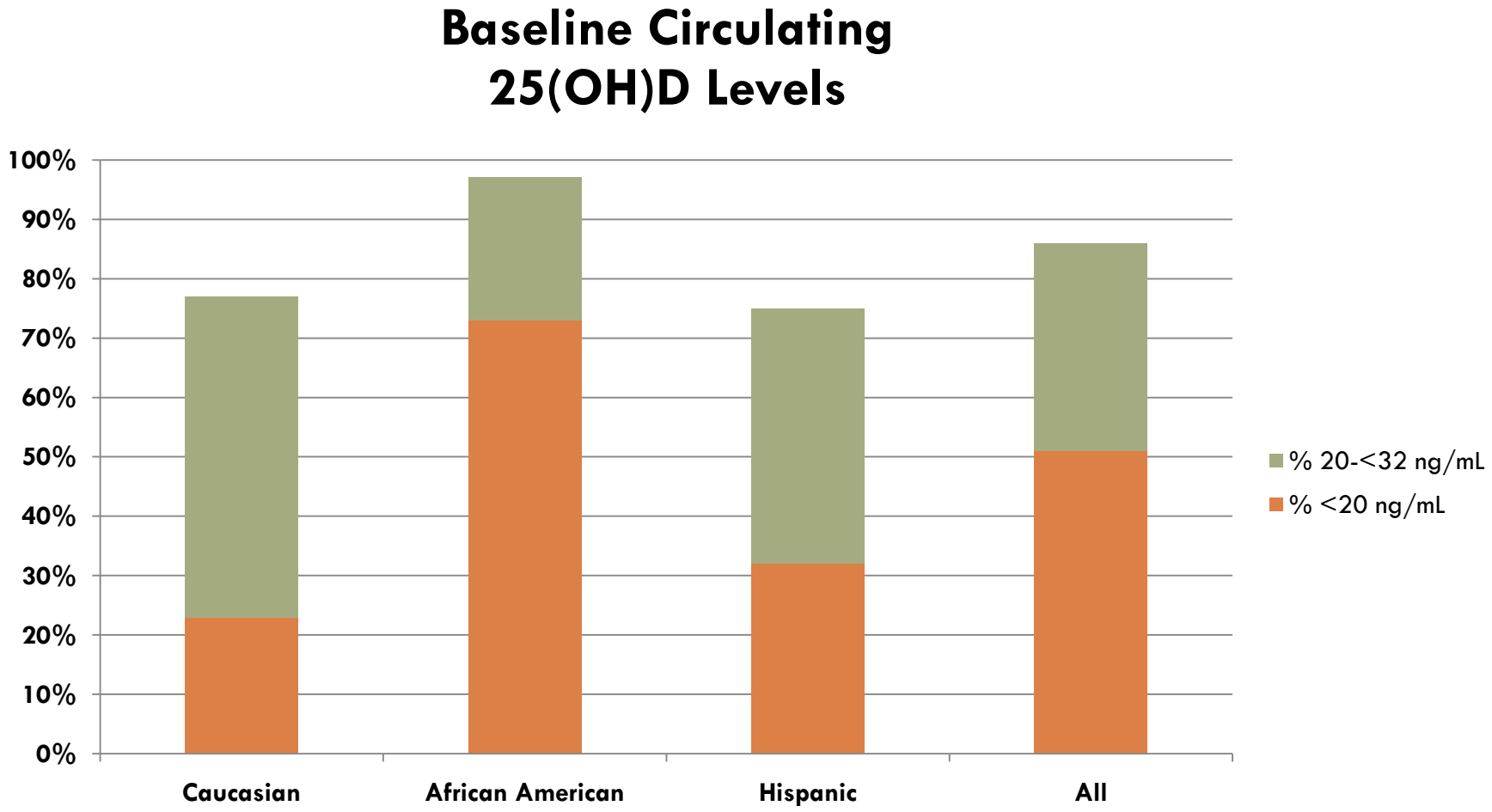
I have no financial interest to disclose with regard to this presentation.

What we will cover today…

- Why are we deficient in vitamin D?
- What is optimal and what is not?
- Link between vitamin D and other long latency diseases—role of the innate immune system
- Issues specific to pregnancy, lactation & early infancy

Evidence of the Epidemic



Why is vitamin D deficiency so prevalent?

THE DANGERS OF VITAMIN D

Committee on Nutrition, Pediatrics, 1963

Interesting Facts

- Concern in 1950's that vitamin D given to pregnant women was teratogenic
- Concern that even for some individuals doses of vitamin D above 400 IU/day could be toxic
  - In 1964, no quantitative means of assessing circulating concentrations of vitamin D
    - In fact, at that time, unproven that vitamin D was further metabolized within the body
- By 1967, vitamin D was viewed by the medical community as a significant causative factor in Supravalvular Aortic Stenosis Syndrome (SAS)
  - Taussig, H.B. 1966. Possible injury to the cardiovascular system from vitamin D. *Ann Intern Med* 65:1195-1200.
  - Friedman, W.F. 1967. Vitamin D as a cause of the supravalvular aortic stenosis syndrome. *Am Heart J* 73:718-720.

SAS Syndrome—the Dogma

- **Premise: Maternal vitamin D supplementation during pregnancy caused SAS syndrome, the elfin facies and other findings described**
- Animal models were developed to show that toxic excesses of vitamin D during pregnancy would result in SAS
  - Antia, A.V., Wiltse, H.E., Rowe, R.D., Pitt, E.L., Levin, S., Ottesen, O. E., and Cooke, R.E. 1967. Pathogenesis of the supravalvular aortic stenosis syndrome. *J. Pediatr* 71:431-441.
  - Seelig, M. 1969. Vitamin D and cardiovascular, renal and brain damage in infancy and childhood. *Ann NY Acad Sci* 147:537-582.
- Pharmacologic doses of vitamin D (hundreds of thousands of IU) were given to animals creating hypervitaminosis D with hypercalcemia.

What we were to find out…

- That SAS was not caused by too much vitamin D *per se*
  - But what, in fact, is a genetic disorder called Williams Syndrome

Williams Syndrome

- A severe genetic affliction related to elastin gene disruption
  - Caused by deletion of elastin and contiguous genes on chromosome 7g11.23
- Characterized by multiorgan involvement (including SAS), dysmorphic facial features, and a distinctive cognitive profile

Misattribution of vitamin D as the cause of SAS

- Williams Syndrome patients often exhibit abnormal vitamin D metabolism
  - Exaggerated response of circulating 25(OH)D to orally administered vitamin D
  - Susceptible to bouts of idiopathic hypercalcemia
    - Morris, C.A., and Mervis, C.B. 2000. William's syndrome and related disorders. *Ann Dev Genomics Human Genet* 1:461-484.
  - This relationship was suspected as early as 1976 but was not definitively made until 1991:
    - Becroft, D.M.O., and Chambers, D. 1976. Supravalvular aortic stenosis-infantile hypercalcemia syndrome: in vitro hypersensitivitiy to vitamin D and calcium. *J. Med. Genetics* 13:223-228.

Second Problem: What constitutes sufficiency?

- Even today we do not know full what is sufficiency for infants, children and adolescents—we are just beginning to learn
- View that vitamin D was needed most for growing bones, i.e. in children with little requirement beyond childhood
  - For adults, the requirement was set at 200 IU vitamin D/day—which was viewed as a 'liberal amount'.
    - *National Academy of Sciences. Recommended dietary allowances*. 1989 Washington, D.C.: National Academy Press.
- The premise: all that one needed could be obtained from one glass of milk or sticking your arm out of the car window for 10 minutes three times a week.

What is the optimal circulating concentration of 25(OH)D in humans?

- An office worker, covered in sunscreen, inactive, general sun paranoia (2-15 ng/mL)
- Field worker (40-70 ng/mL)
- Lifeguard (60-90 ng/mL)
- A Pregnant woman and her developing fetus???
- A lactating woman and her breastfeeding infant???
- Children from early childhood through adolescence???

Haddad and Chyu, JCEM 1971, 33: 992-995

Group	No.	Age (years)	Consumption Of D Weekly (units)	Weekly Exposure to Sunlight (hours)	Plasma 25 – HCC (ng/ml)
Normal Adult Volunteers	40	30.2 ± 12.9	2230 ± 1041	8.8 ± 6.1	27.3 ± 11.8
Biliary Cirrhosis	4	1.5 - 55	2500 (est.)	_____	6.4 ± 2.6*
Lifeguards	8	18.5 ± 2.0	2895 ± 677	53.0 ± 10.3	64.4 ± 8.7*

* P < .001

+ values represent mean ± SD

Haddad and Chyu article

This article became the basis for "normal vitamin D status" in humans.

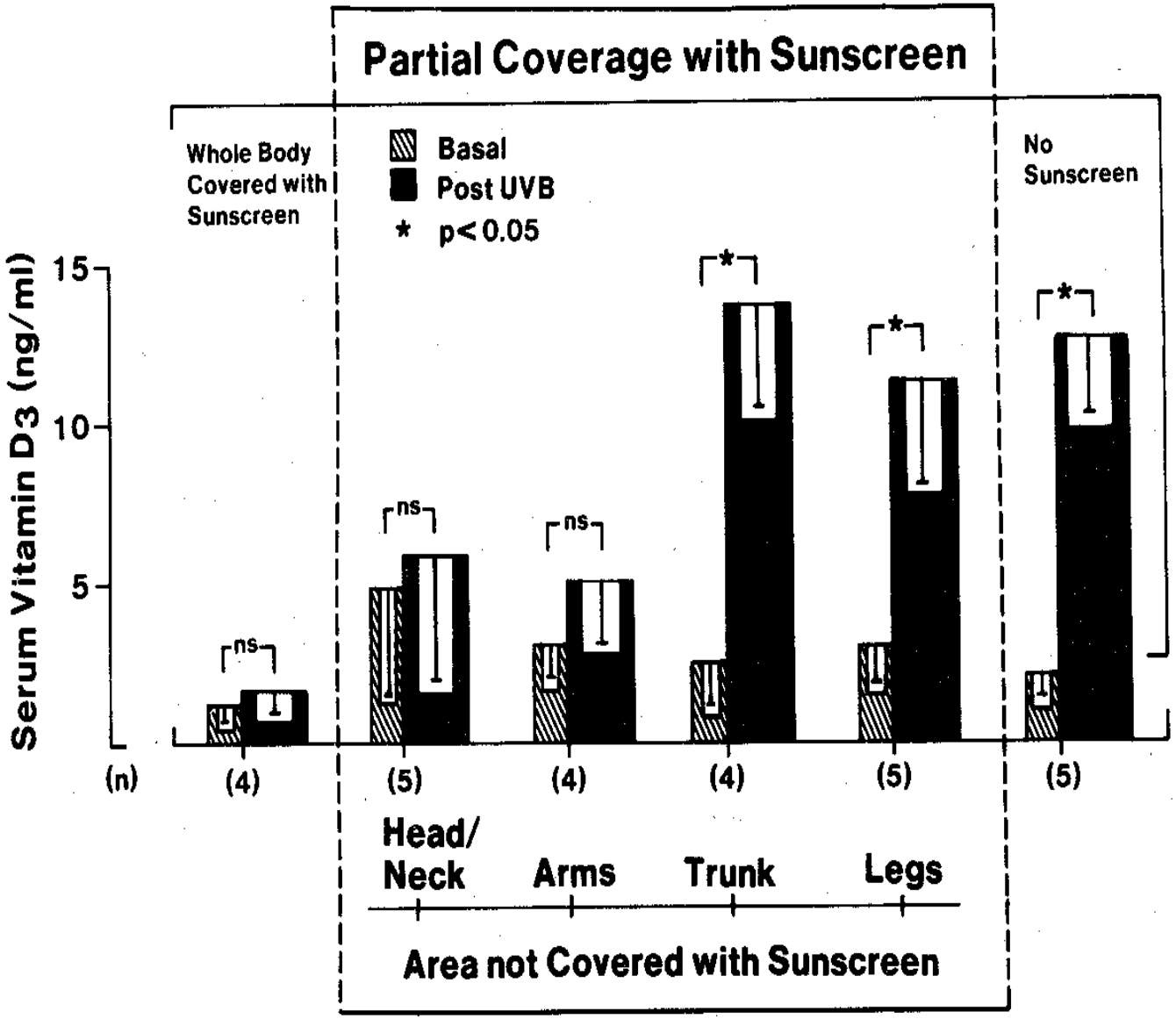
It was not powered to do so and was actually describing a method to measure 25(OH)D reliably and more easily in the laboratory.

“Normal” Vitamin D Status

- Should NEVER have been defined by Gaussian distribution
- This is similar to defining “normal” estrogen levels by sampling a population of women who are primarily postmenopausal.
- There is a range that is associated with better health below which there are higher rates of disease states—we know this in 2009—we did not know this even five years ago.

Problem #3—

Sunscreen and Lifestyle Changes



Matsuoka, L.Y., Wortsman, J., and Hollis, B.W. 1990. Use of topical sunscreen for the evaluation of regional synthesis of vitamin D_3. *J Amer Acad Dermatol* 22:772-775.

Adequate Intake for Vitamin D

- Children: 400 IU/d approximated from one teaspoon of cod-liver oil

  (Park, JAMA 1940:115:370-9)

  Even today, this is sound advice when you look at it on a per kilogram basis.

- Adults: One-half (200 IU)/d the infant dose to ensure that adults obtain some from the diet

  (Blumberg et al, Pediatrics 1963;31:512-25)

  - Considered a "generous allowance" in the 1989 version of the American recommended dietary allowances

Indoor Air Quality Act of 1989

- Average American spends 93% of their time indoors
- Profound implications for endogenous synthesis of vitamin D_3
  - 1989. Report to Congress on Indoor Air Quality, Volume II: Assessment and Control of Indoor Air Pollution. Office of Air and Radiation. U.S. Environmental Protection Agency EPA 400-1-89-001C, pp. I, 4-14

What determines your vitamin D status?

- Degree of skin pigmentation
- Sunlight exposure
- Dietary contribution (<10% total)
- Latitude
- Season/time of year and angle of sun's rays
- Use of sunscreen or protective or full clothing
- Outdoor exposure
- Body Mass Index
  - BMI >30 associated with decreased circulating 25(OH)D as fat serves as a vitamin D reservoir

What determines your vitamin D status if you are a fetus or neonate?

- Neonatal vitamin D status direct reflection of maternal status
- Neonatal levels are ~0.6-0.7 of maternal levels
- In Charleston, SC, 100 cord blood samples were collected at delivery:
  - Mean gestational age: 37.4 $\pm$ 3.2 weeks (range 27-41; median 38).
  - > 80% of the cohort delivered greater than 37 weeks' gestation.
  - 25(OH)D mean $\pm$ SD for the cohort: 13.5 $\pm$ 8.3 ng/mL.
  - By race, there were significant differences between groups ($p<0.0001$)

Basile LA, et al. J Perinatology 2007

Cord Blood 25(OH)D by Season and Race

Group	All Year	April 1 – October 31	November 1 – March 31
All	13.5 ± 8.3 (n=100)	19.5 ± 9.6 (n=15)*	12.3 ± 7.7 (n=83)
African American	10.5 ± 6.0 (n=67)*	13.1 ± 4.0 (n=9)	10.1 ± 5.7 (n=58)*
Caucasian	19.5 ± 9.6 (n=33**)*	29.0 ± 7.0 (n=6)*	17.7 + 9.2 (n=25)*

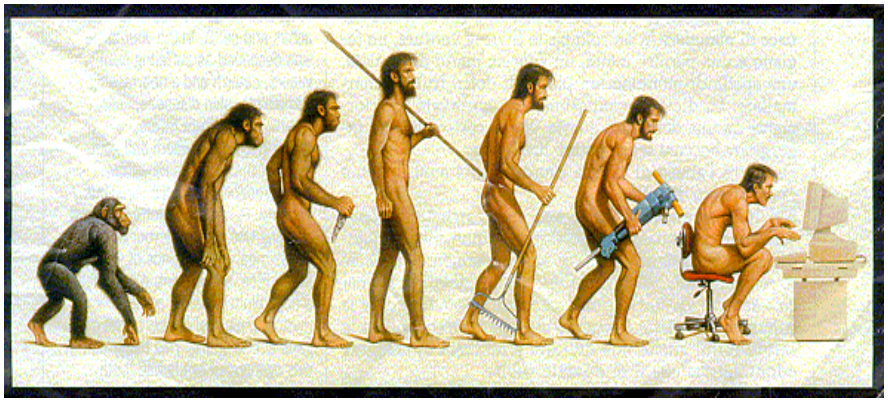
***p value< 0.0001; **season missing for 2 cases**

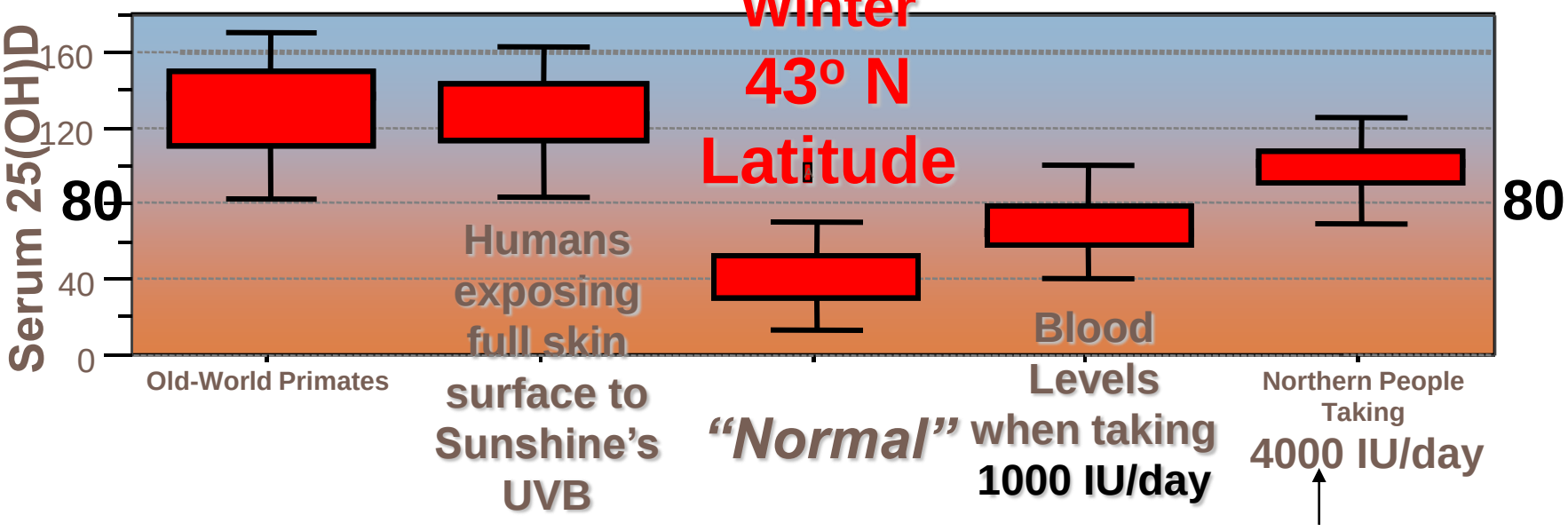
Basile L, Taylor S, Quinones L, Wagner C, Hollis B 2007 Neonatal vitamin D status at birth at latitude 32º72': Evidence of widespread deficiency. J Perinatology **27**(9)**:**568-571.

Substrate Deprivation

- Why are maternal and neonatal vitamin D levels so low?
- The vitamin D endocrine system is the ONLY steroid endocrine system in the body that is almost always limited by substrate availability due to latitude, lifestyle, race etc.
  - Vitamin D conversion to 25(OH)D
  - 25(OH)D conversion to $1,25(OH)_2D$ in extra-renal sites

Vitamin D Status in Primates and Early Humans





Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000

Stages of Vitamin D Deficiency in Infants

Stage I: Hypocalcemia & euphosphatemia

Stage II: Eucalcemia, hypophosphatemia, & slight increase in skeletal alkaline phosphatase

Stage III: Hypocalcemia, hypophosphatemia, & increased alkaline phosphatase

Consequences of Vitamin D Insufficiency

Calcium absorption[1]

- When vitamin D status is sufficient, absorption of dietary calcium is approximately 30% to 40%.
- As vitamin D status declines, absorption of dietary calcium declines to about 10% to 15%.

PTH

- Low levels of vitamin D leads to increased release of PTH,[2] which increases bone resorption and decreases bone mass.

Bone Mass

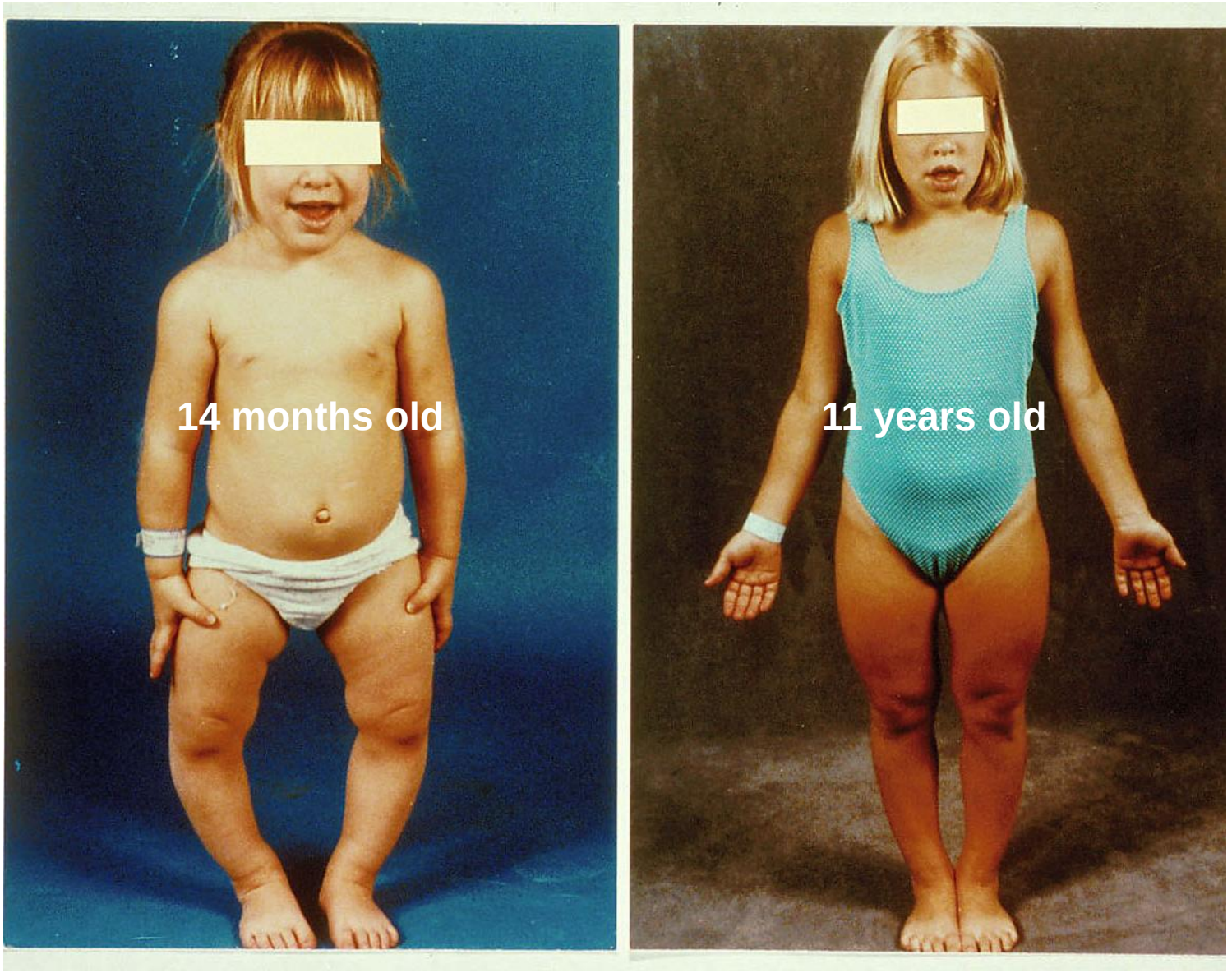
- Given its effect on calcium absorption, vitamin D insufficiency is associated with bone loss and an increased fracture risk.

1. Holick MF. *Curr Opin Endocrinol Diabetes.* 2002;9:87–98; Lips P. *Endocr Rev.* 2001;22:477–501.
2. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357(3): 266-281.

Vitamin D Deficiency

- Rickets
  - Enlargement of skull, joints of long bones and rib cage, curvature of spine and thighs, generalized muscle weakness
- Osteomalacia
- Immune
  - Immunomodulatory actions
    - Potent stimulator of innate immune system acting through toll-like receptors on monocytes and macrophages
  - Cancers – leukemia, prostate & breast cancer, psoriasis, diabetes mellitus

Classic Rickets: Obvious deformities correctable but what about other risks?



Photos courtesy of Dr. Lyndon Key, MUSC

How toxic is vitamin D?

- The U.S. Nutrition Guidelines state that the lowest observed adverse effect level (LOAEL) for humans is 2,000 IU vitamin D/day

Finland - Historical

Recommended intake of Vitamin D for Infants in Finland

- 1950s – 1964 4000-5000 IU/d
- 1964 2000 IU/d
- 1975 1000 IU/d
- 1992 400 IU/d

*No infantile hypercalcemia reported

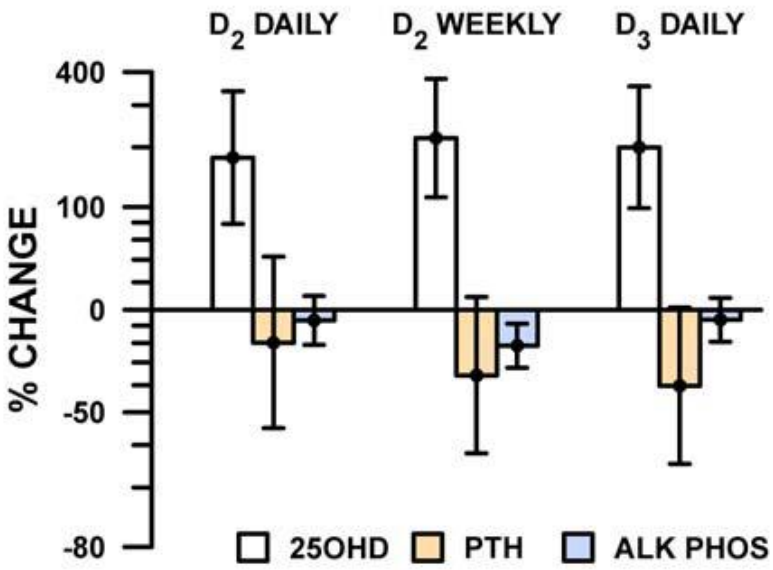
- Follow-up of these children 30+ years later shows lower rates of type I diabetes in those who received at least 2000 IU vitamin D/day as infants

A series of landmark studies—focus on safety and redefining the LOAEL

- Vieth, R. 1999. Vitamin D supplementation, 25-hydroxy-vitamin D concentrations, and safety. *Am J Clin Nutr* 69:842-856.
- Vieth, R., Chan, P.C.R., and MacFarlane, G.D. 2001. Efficacy and safety of vitamin D_3 intake exceeding the lowest observed adverse effect level (LOAEL). *Amer J Clin Nutr* 73:288-294.
- Heaney RP, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003; 77:204-210.

Gordon CM et al: Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab 2008

- 6-wk supplementation with 2000 IU D_2/day, 50000 IU D_2 weekly or 2000 IU D_3/day
- Three regimen were equivalent in raising 25(OH)D levels with minimal change in serum calcium and equivalent decreases in PTH



Biomarkers for Vitamin D Sufficiency

- 25(OH)D
- Intact PTH
- Bone Mineral Density (BMD)
- Intestinal Calcium Absorption
- Mobility responsiveness
- Insulin sensitivity
- Beta cell function
- Immune function
- ???Presence or absence of long-latency diseases such as diabetes, rheumatoid arthritis, MS, prostate and breast cancers, cardiovascular diseases

Acute and Long Latency Diseases

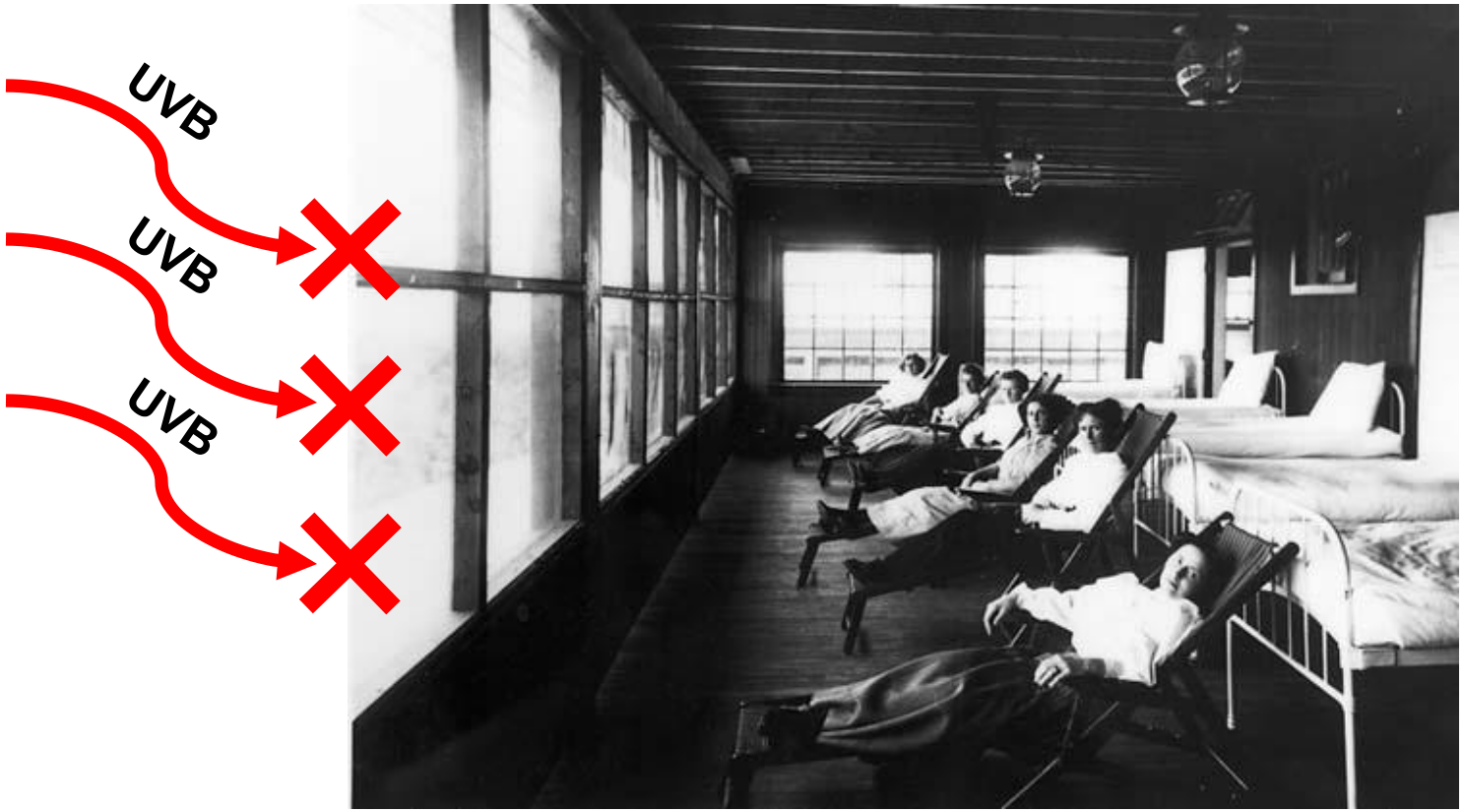
- Flu, acute respiratory infections, tuberculosis
- Various types of cancers, including colon, prostate, and breast cancers
- Autoimmune diseases such as Lupus, Multiple Sclerosis, Rheumatoid Arthritis, Scleroderma
- Type 1 Diabetes; Type 2 diabetes, insulin resistance and obesity
- Osteopenia, osteomalacia and rickets
- Cardiovascular disease
- Fetal growth, fetal dentition, and bone mass
  - And the list goes on…

What do these diverse groups of disease states all have to do with vitamin D?

Vitamin D and the Innate Immune System

- In 1903, Niels Ryberg Finsen was awarded the Nobel Prize for his work, demonstrating that UV light was beneficial to patients with Lupus vulgaris.
- The beneficial effects of UV exposure to tuberculosis patients is also known.

Yet, what went wrong with sanatoriums?

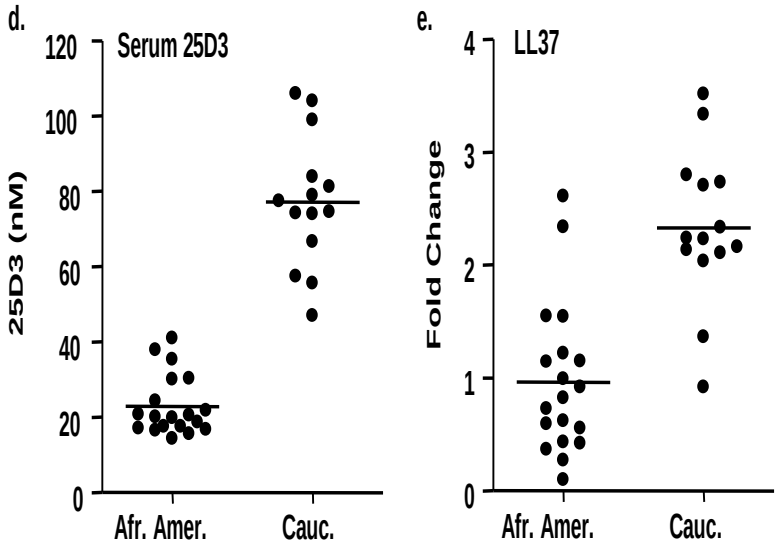


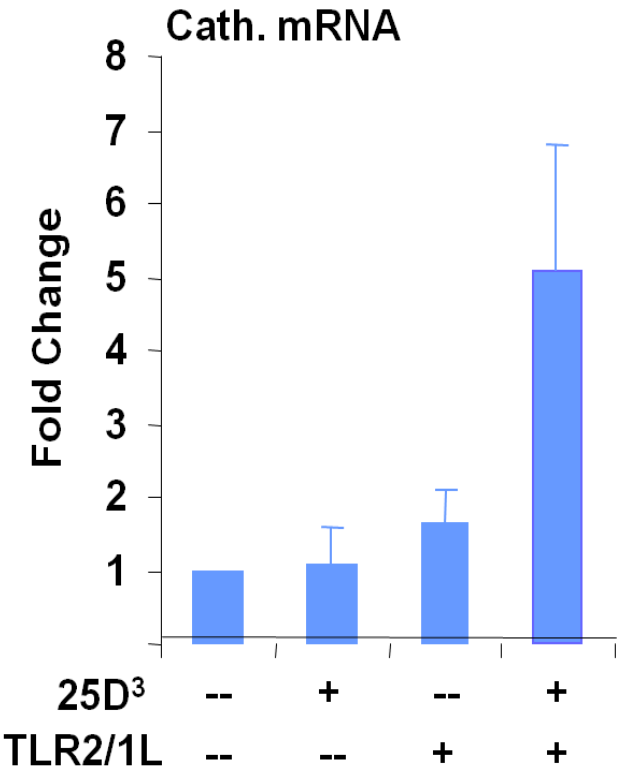
Cathelicidin (LL-37)

- An endogenous antimicrobial peptide
- Generated by innate immune system in response to microbial invasion thru Toll 2 surface receptor on monocytes and macrophages
  - Vitamin D Responsive Element (VDRE) also contained in gene regulatory region of these cell types

Sera taken from AA subjects with low 25(OH)D inefficient in supporting cathelicidin mRNA induction

- Addition of 25(OH)D_3 restores ability of sera from AA to mediate induction of cathelicidin mRNA





Liu P, et al. Toll-like receptor triggering of a vitamin-D mediated human antimicrobial response. Science 2006; 311

- Support a link between TLRs and vitamin D–mediated innate immunity
- Suggest differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection

It also explains these findings—of rickets and infection

- Rickets is not only associated with skeletal abnormalities but also respiratory infections.
- In 1994 a brief study demonstrated that respiratory infections in children with elevated alkaline phosphatase levels were eliminated by supplementing them with 60,000 IU vitamin D/wk for a period of 6 wks.

Rehman P 1994 Sub-clinical rickets and recurrent infection. J Tropical Pediatr **40:**58.

Vitamin D and Pregnancy

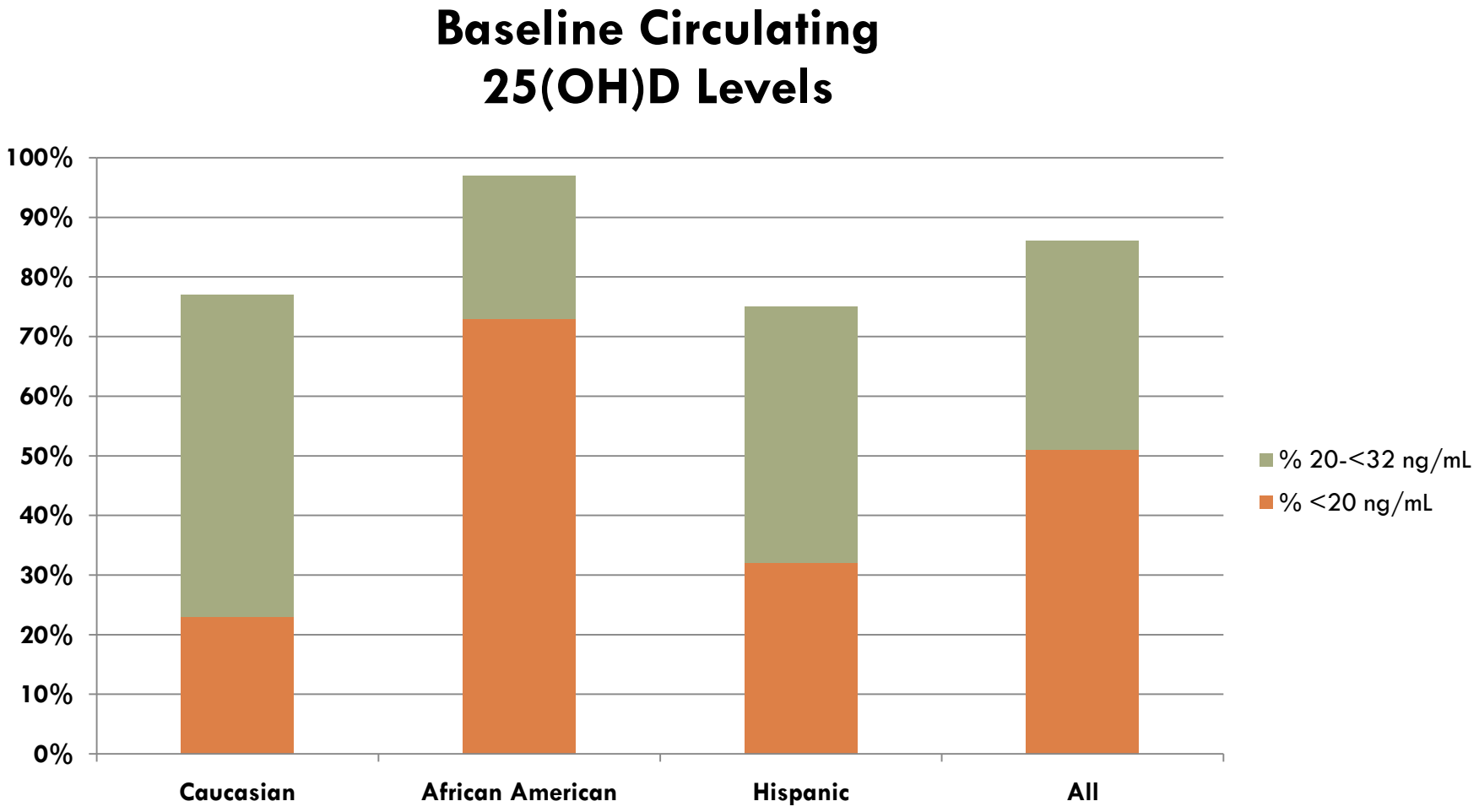
Much consternation—Vitamin D deficiency is not limited to children

- Nesby-O'Dell, S., Scanlon, K., Cogswell, M., Gillespie, C., Hollis, B., Looker, A., Allen, C., Doughertly, C., Gunter, E., and Bowman, B. 2002.
- Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey: 1988-1994. *Am J Clin Nutr* 76:187-192.

What was known in 2002…

- A subset of pregnant women had or developed vitamin D deficiency during their pregnancy
  - Adverse effects known in terms of impaired fetal growth, dentition, lighter/less dense bones, and rarely, neonatal seizures from profound hypocalcemia
- Supplementation with vitamin D beyond 400 IU/day was unnecessary and risky—
  - Remember the teratogenicity data
- A scientific review committee at NIH reviewed our grant to evaluate the vitamin D requirements of the pregnant woman and thought the study worthy of doing.
  - It began a cascade of events that has changed the way we view vitamin D today.

Evidence of the Epidemic: Our Data in South Carolina



Deficiency during Fetal & Infant Development

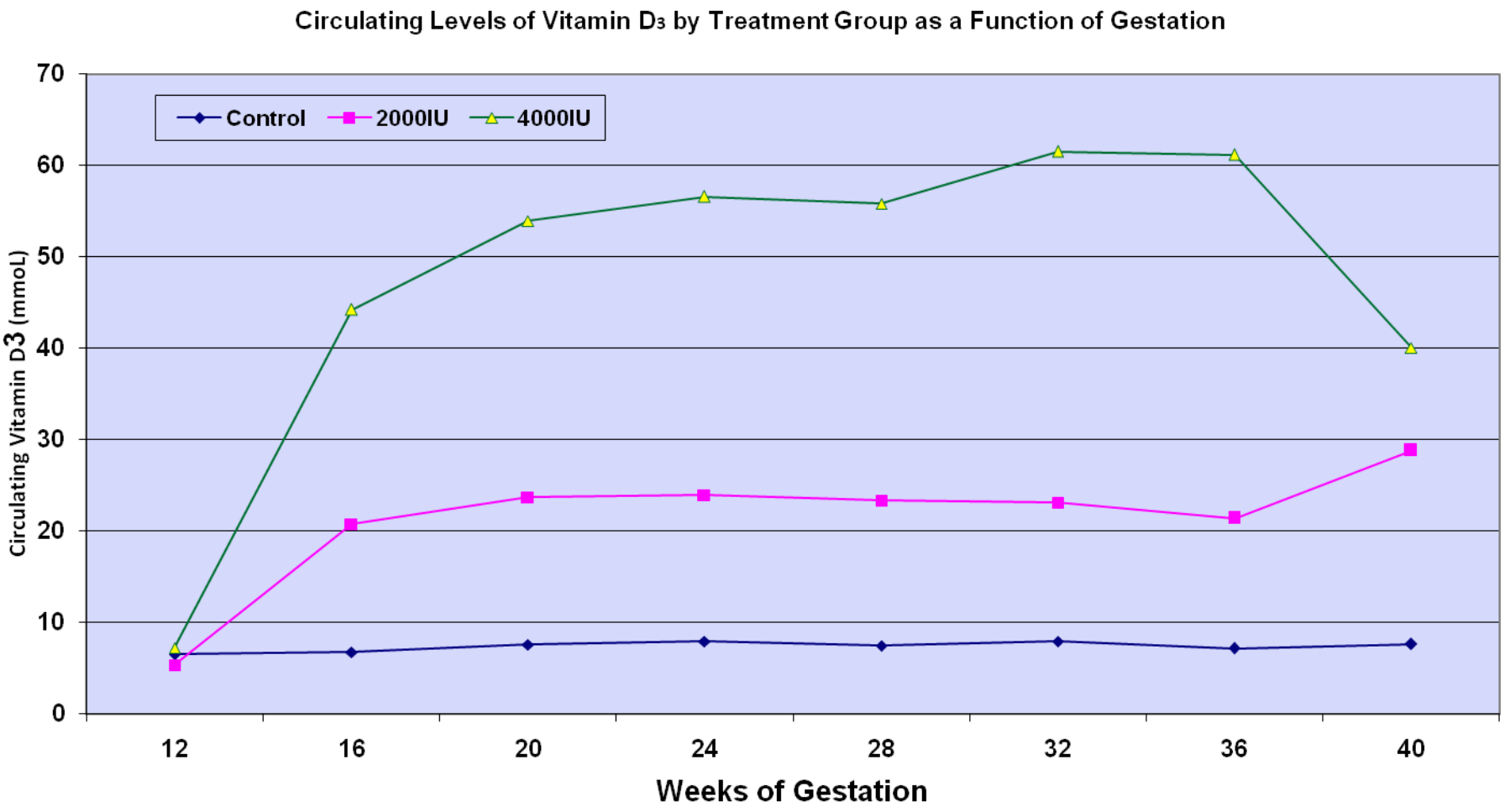
- **Higher risk of maternal preeclampsia**
  - Halhali A, Tovar AR, Torres N, Bourges H, Garabedian M, Larrea F 2000 Preeclampsia is associated with low circulating levels of insulin-like growth factor 1 and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. J Clin Endocrinol **85**(5):1828-2833.
  - Hypponen E 2005 Vitamin D for the prevention of preeclampsia? A hypothesis. Nutr Rev **63**(7):225-32.
  - Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM 2007 Maternal Vitamin D Deficiency Increases the Risk of Preeclampsia, vol. 92, pp 3517-3522.
- **Impaired fetal growth**
  - Brooke OG, Brown IRF, Bone CDM, Carter ND, Cleeve HJW, Maxwell JD, Robinson VP, Winder SM 1980 Vitamin D supplements in pregnant Asian women: Effects on calcium status and fetal growth. Brit Med J **1**:751-754.
  - 6Brunvand L, Quigstad E, Urdal P, Haug E 1996 Vitamin D deficiency and fetal growth. Early Human Development **45**:27-33.
- **Impaired dentition**
  - Purvis RJ, Barrie WJ, MacKay GS, Wilkinson EM, Cockburn F, Belton NR 1973 Enamel hypoplasia of the teeth associated with neonatal tetany: a manifestation of maternal vitamin-D deficiency. Lancet **2**(7833):811-4.
- **Increased risk of gingivitis and periodontal disease**
  - Dietrich T, Nunn M, Dawson-Hughes B, Bischoff-Ferrari HA 2005 Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. Am J Clin Nutr **82**:575-580.
  - Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA 2004 Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr **80**(1):108-13.
- **At this time, not known about other rates of infection or other long-term markers**

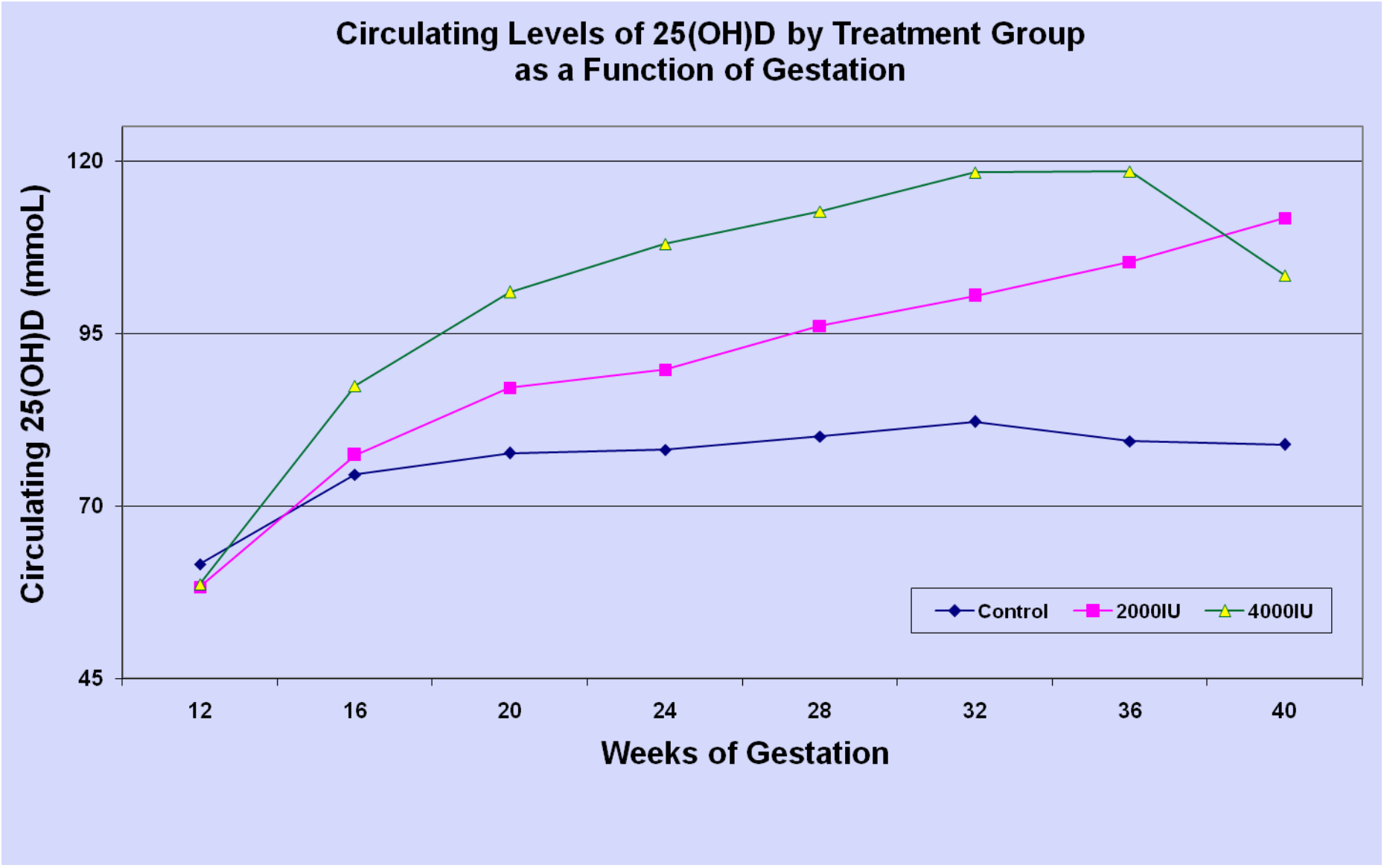
FDA IND #66,346 Hollis, Bruce W.

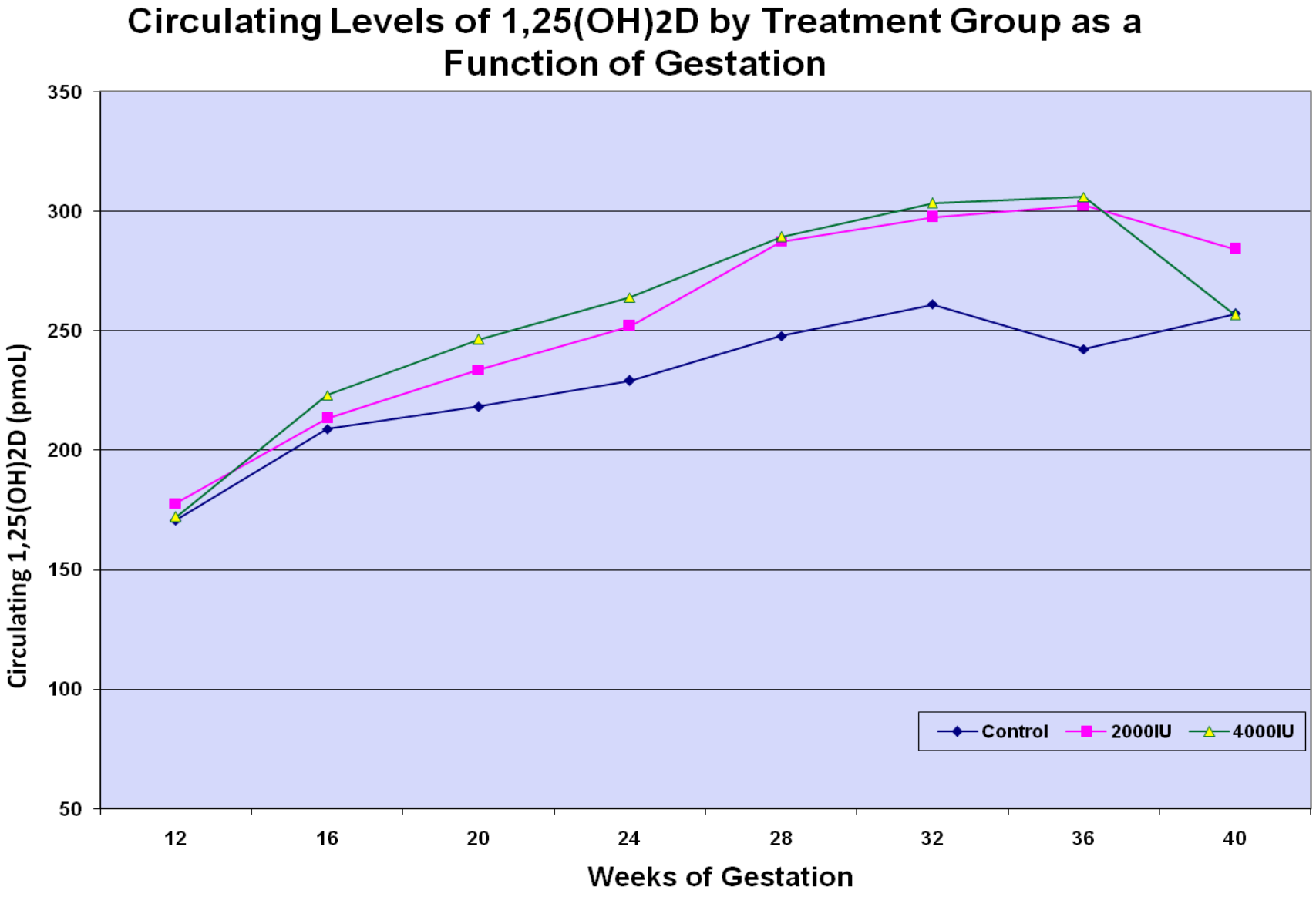
- 2003: First time in its history that the FDA regulated a vitamin—there have been other INDs for vitamin D granted since then
- Required to conduct research in the U.S. when using high dose vitamin D supplementation therapy
- Underscores the fear that exists about vitamin D toxicity and the need for careful study
  - However more difficult it may have been to receive, it adds to the scientific rigor of any study

NICHD-Supported Study

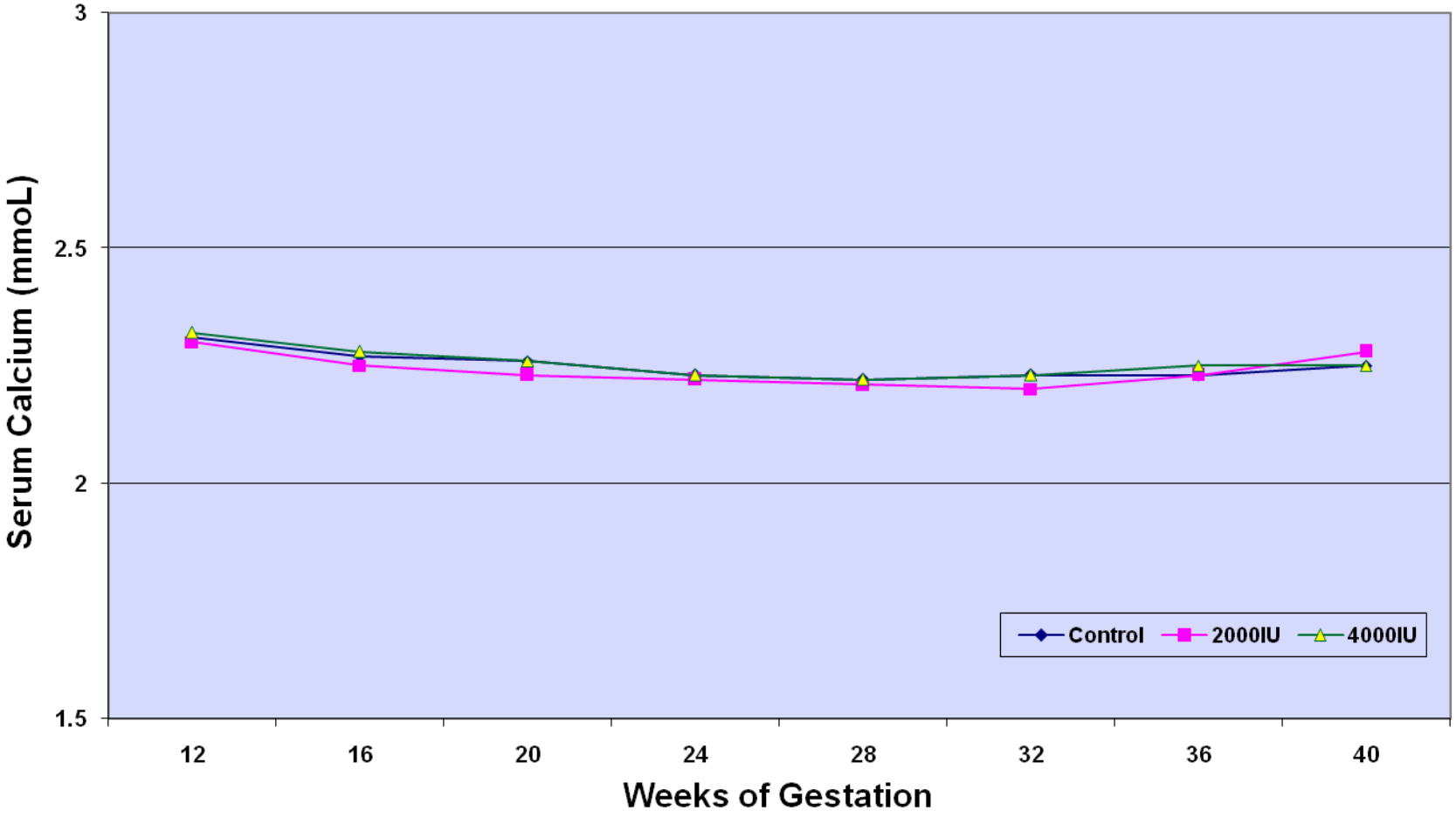
- 510 women enrolled
- Randomized to one of three treatment groups:
  - 400 IU vitamin D_3/day
  - 2000 IU vitamin D_3/day
  - 4000 IU vitamin D_3/day
- Monthly vitamin D, calcium and urine Ca/Cr ratios monitored
- 336 women and infants being followed for 1 yr after delivery
- No adverse events related to vitamin D toxicity—no hypercalciuria and no hypercalcemia
- Study completed in July 2009
- (*Safety and outcomes data abstracts accepted by Pediatric Academic Societies, platform presentations May 2&3, 2010, Vancouver, Canada*)


Circulating Levels of Vitamin D3 by Treatment Group as a Function of Gestation
Control
2000IU
4000IU
Circulating Vitamin D3 (mmoL)
70
60
50
40
30
20
10
0
12
16
20
24
28
32
36
40
Weeks of Gestation

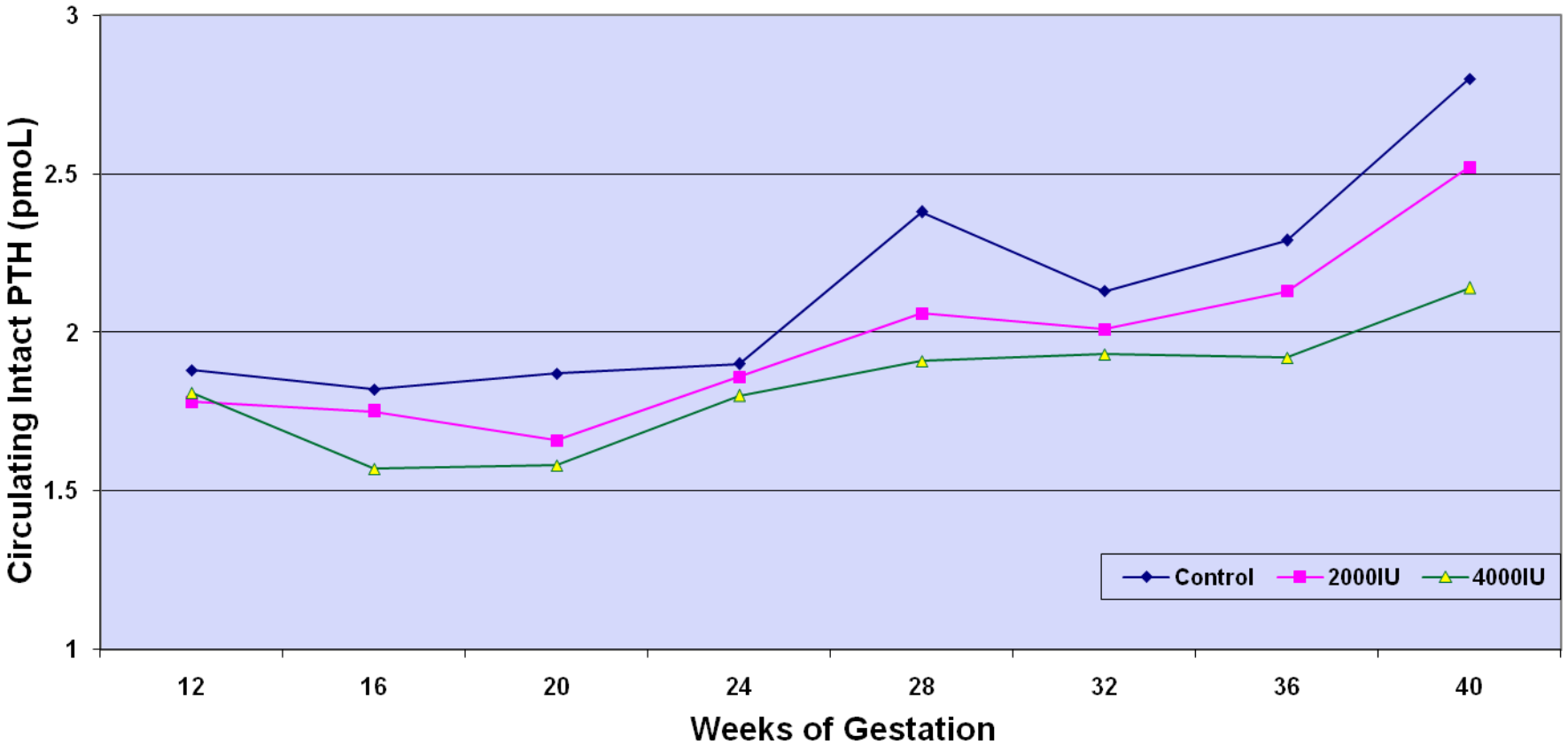

Circulating Levels of 25(OH)D by Treatment Group
as a Function of Gestation
Circulating 25(OH)D (mmoL)
120
95
70
45
12
16
20
24
28
32
36
40
Weeks of Gestation
Control
2000IU
4000IU

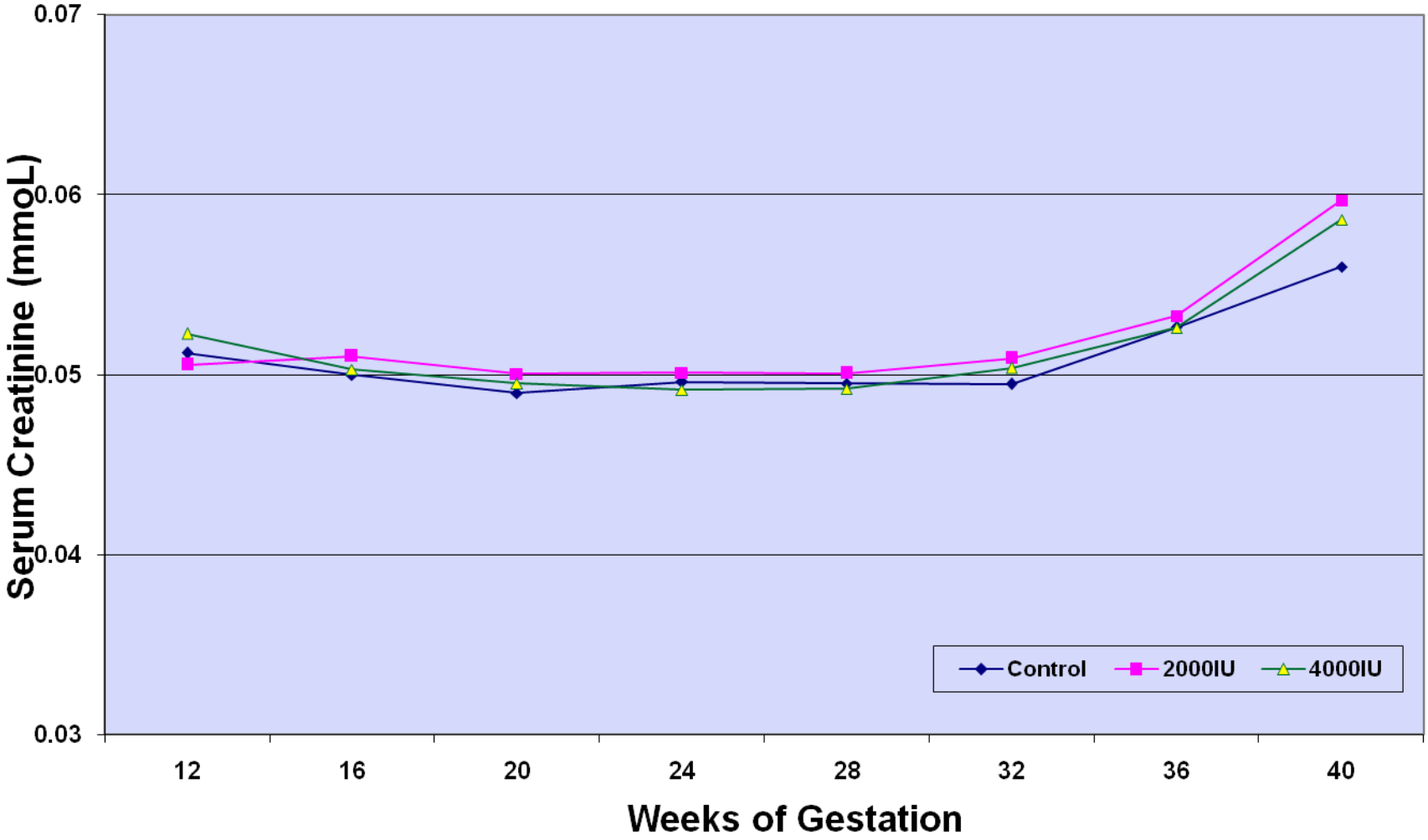

Circulating Levels of 1,25(OH)2D by Treatment Group as a Function of Gestation
Circulating 1,25(OH)2D (pmoL)
350
300
250
200
150
100
50
12
16
20
24
28
32
36
40
Weeks of Gestation
Control
2000IU
4000IU

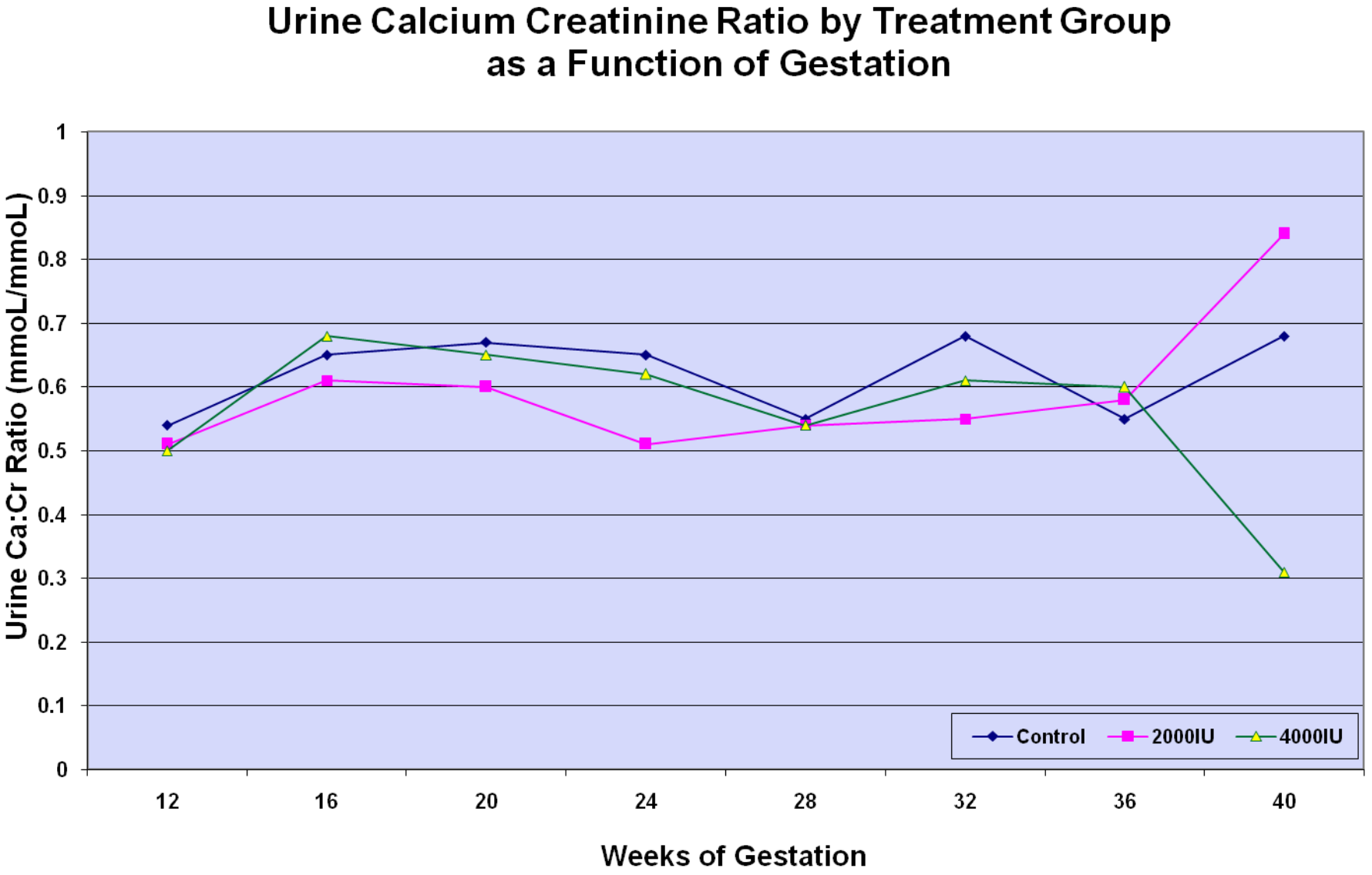
Serum Calcium Levels by Treatment Group as a Function of Gestation



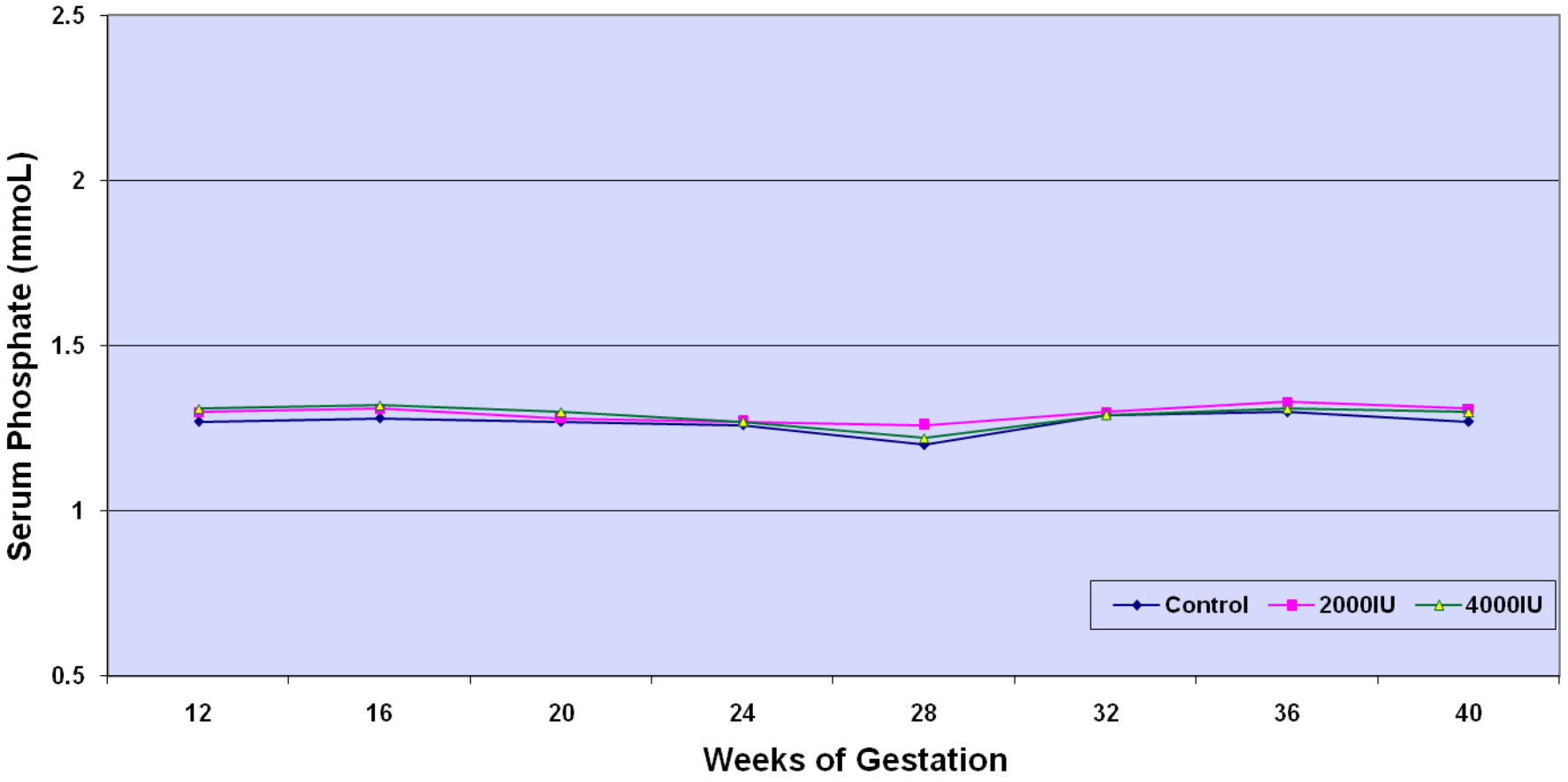
Circulating Intact Parathyroid Hormone (iPTH) byTreatment Group as a Function of Gestation



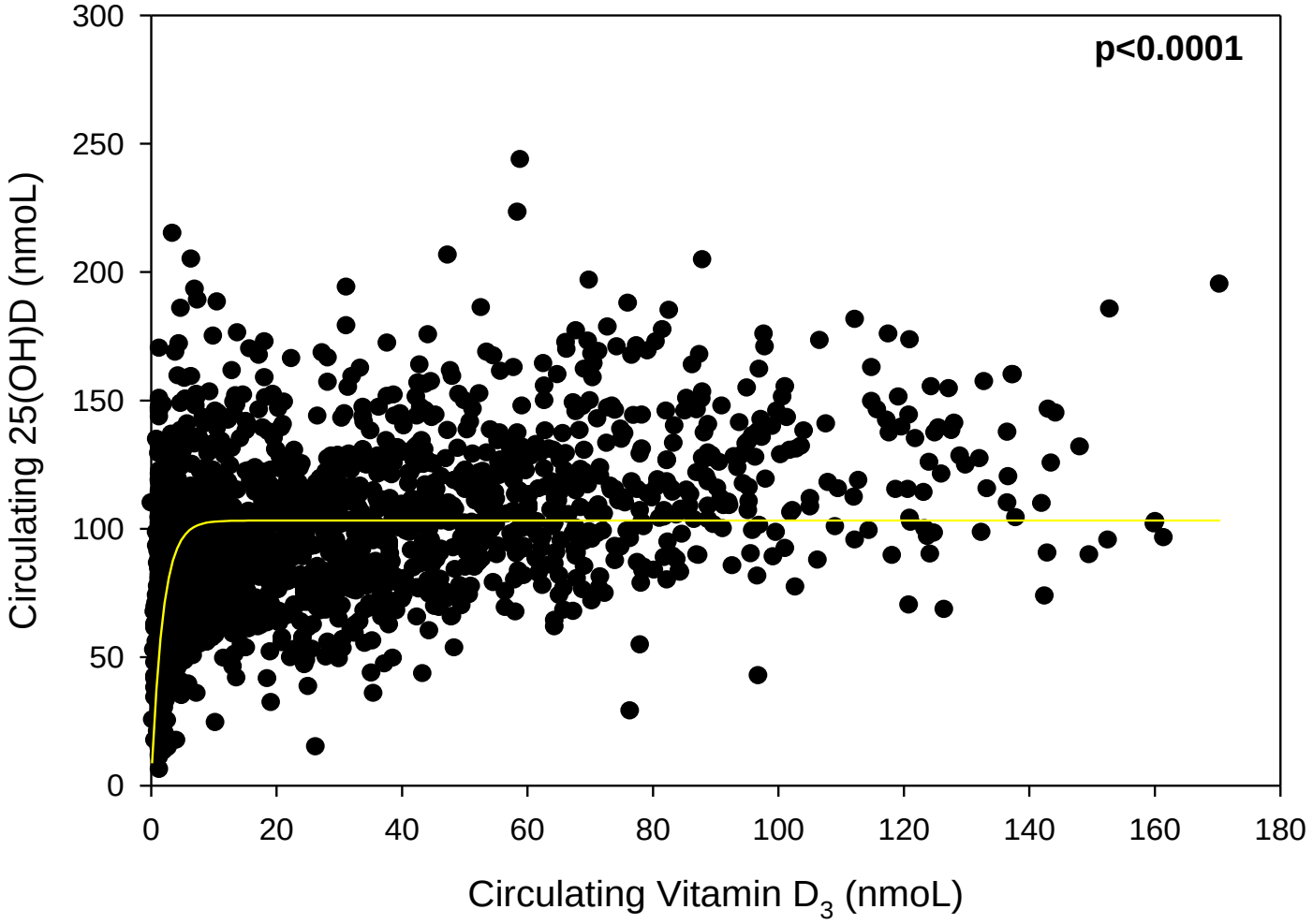

Serum Creatinine Levels by Treatment Group
as a Function of Gestation
Serum Creatinine (mmoL)
0.07
0.06
0.05
0.04
0.03
12
16
20
24
28
32
36
40
Weeks of Gestation
Control
2000IU
4000IU


Urine Calcium Creatinine Ratio by Treatment Group as a Function of Gestation
Urine Ca:Cr Ratio (mmoL/mmoL)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
12
16
20
24
28
32
36
40
Weeks of Gestation
Control
2000IU
4000IU

Serum Phosphate Levels by Treatment Group as a Function of Gestation

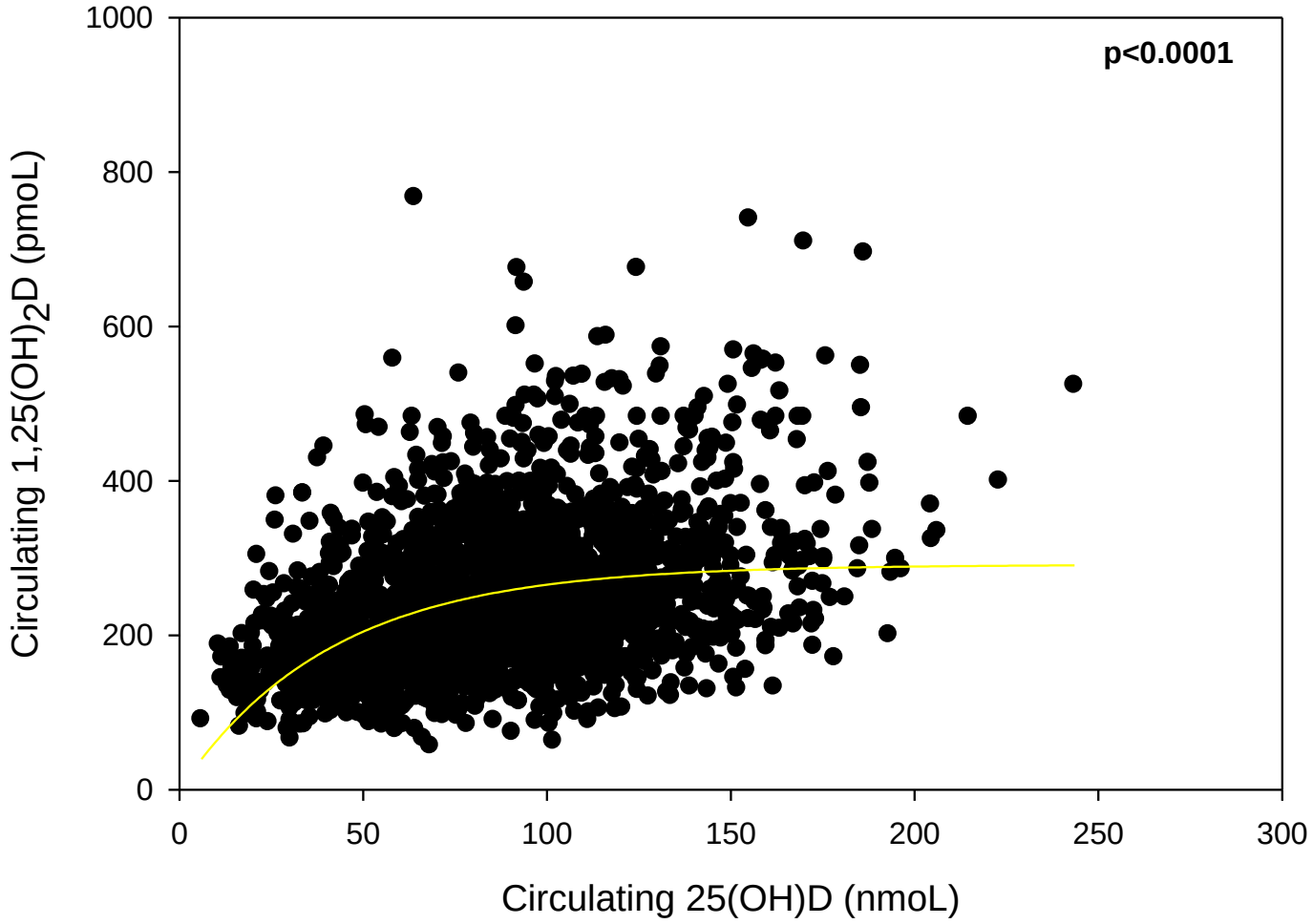


Relationship of Circulating Vitamin D_3 on Circulating 25(OH)D During Pregnancy



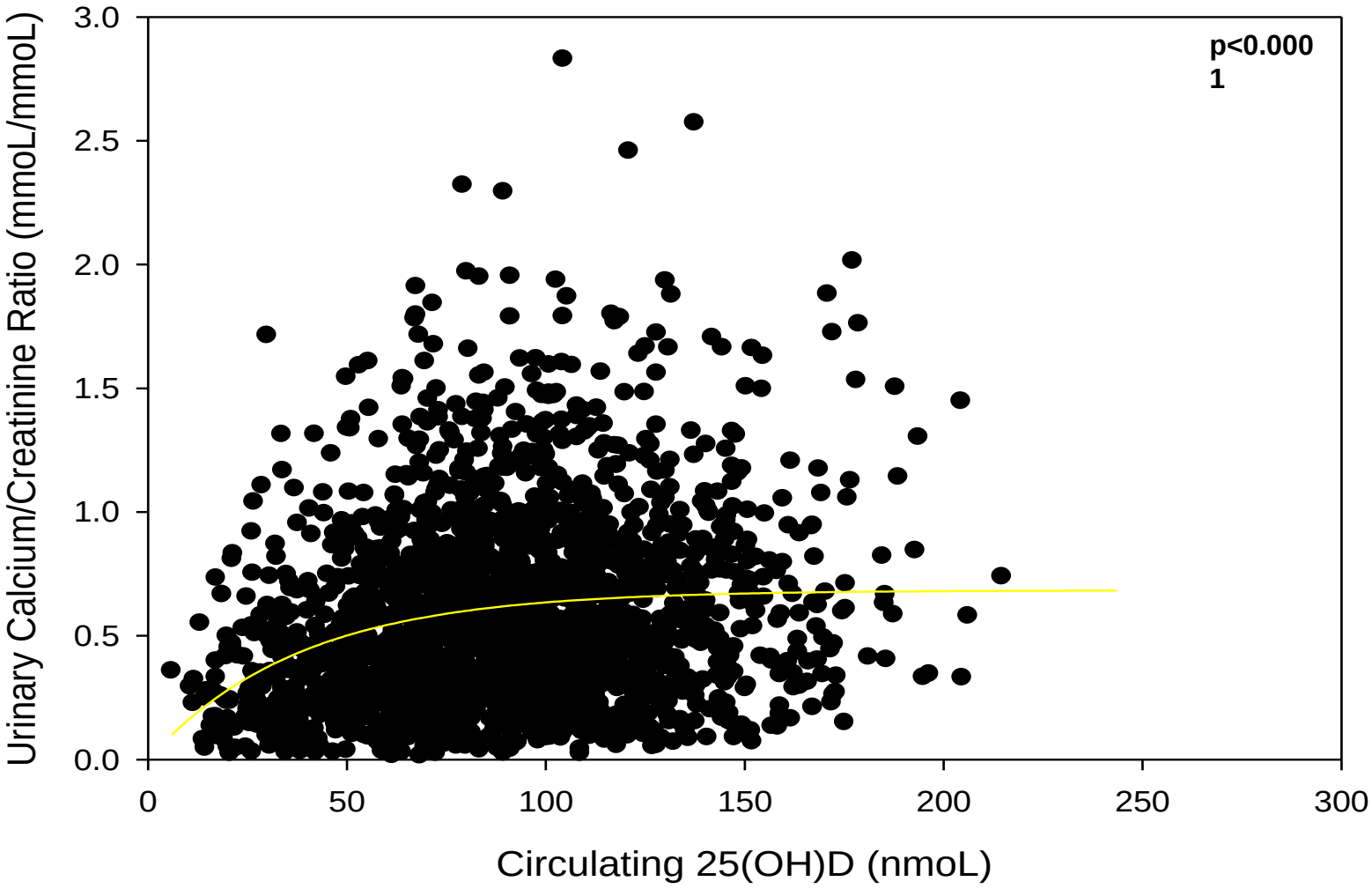
$25(OH)D=103.229 * (1-\exp(-0.541351 * D_3))$

Relationship of Circulating 25(OH)D on Circulating $1,25(OH)_2D$ During Pregnancy



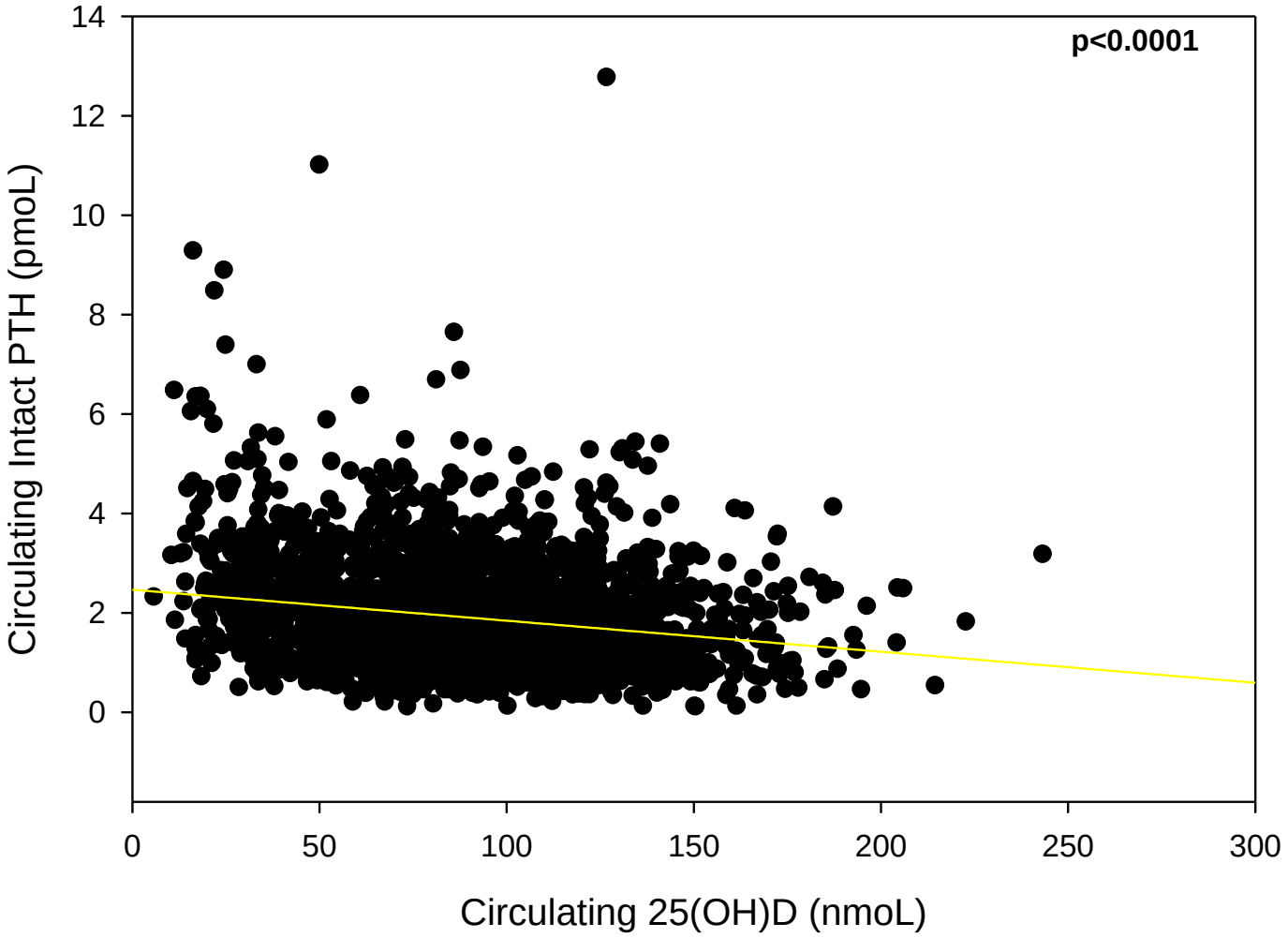
$1,25(OH)_2D=291.231 * (1=exp(-0.0242509 * 25(OH)D))$

Relationship of Circulating 25(OH)D on the Urinary Calcium/Creatinine Ratio During Pregnancy



Urinary Calcium/Creatnine Ratio=0.68384 * (1-exp(-0.0263764 * 25(OH)D))

Relationship of Circulating 25(OH)D on Circulating Intact Parathyroid Hormone During Pregnancy



PTH=2.46597 + -0.00623909 * 25(OH)D

Preliminary Data from NIH Study

- When comparing the control group to the 2000 and 4000 IU groups, there were significant differences on the following parameters:
  (1) Total circulating 25(OH)D levels at visits 3-8 ($p<0.0001$)
  (2) $1,25(OH)_2D$ at visits 3-8 (all comparisons $p<0.05$)
  (3) Preterm labor and preterm delivery ($p<0.0001$)
  (4) Infection ($p<0.0001$)
- The increase from baseline of mothers' levels was greater in the 4000 IU group compared with the 2000 IU group ($p<0.0001$).

Other Findings From NIH Study

- Co-morbidities of pregnancy OR 0.5 (CI 0.27-0.95; p=0.03)
  - 25(OH)D of those with comorbidities was 33.4 vs. 39.0 ng/mL without
  - These remained significant after controlling for race.
- There were no differences between the groups with respect to serum calcium, phosphorus and creatinine levels or urinary calcium/creatinine ratios at any of the visits.
- Further analyses are underway

Preliminary Data from Thrasher Research Fund Study

- The last subject was enrolled on October 31, 2008 and delivered on 5/11/09. Data analysis has begun.
- 257 women consented to participate; 160 continued through delivery.
- Mean baseline 25(OH)D level was 22.7±9.7 ng/mL and did not differ between tx groups (p=0.43), but differed by race:
  - African American 18.5±8.4;
  - Hispanic 26.1±8.4;
  - Caucasian 29.5±14.4 (p<0.0001)
- Monthly Δ: +2.6 ng/mL (95% CL 2.3-2.9); 2.3±0.2 in 2000 and 2.9±0.2 in 4000 IU group (p=0.033)
- Mean neonatal 25(OH)D was 0.7±0.3 that of mothers' at delivery:
  - overall mean 24.5±12.0 ng/mL
  - 22.1±10.3 in 2000- and 27.0±13.3 in 4000 IU group (p=0.024)
  - Correlation between mother and infant: r=0.68 (p<0.001)
- Accepted as poster presentation, Pediatric Academic Societies meeting, May 2010, Vancouver

Thrasher Research Fund Data—Other Findings

- Analysis of pregnancy complications as fx of Δ25(OH)D from baseline, chronic vitamin D status (area under curve), and 1-month prior to delivery:
  - Rates of any infection were inversely related to all 3 measures of vitD status, an effect that persisted even after controlling forrace.
  - Preterm labor/birth was inversely associated with initial (p=0.001) and month prior to delivery 25(OH)D (p=0.008).
- When looking at co-morbidities of pregnancy (preterm labor/delivery [delivery <37 wks], gestational diabetes, pre-eclampsia/eclampsia, or hypertension), higher vitamin D levels were associated with lower risk (OR 0.694, 95% CI 0.506-0.953; p=0.024).
  - When controlling for race, this association persisted: (OR 0.686, CI 0.493-0.953; p=0.025).
- The mean change (SD) from baseline for the 2000 and 4000 IU groups were: +9.95 (11.8) vs. +16.31 (14.0); p=0.0097 adjusted for race.
- No adverse events were associated with vitD supplementation.

Has your infant suffered a cold or upper respiratory tract infection during the last month?

- At **12 months' postpartum,** 111 (50.5%) responded "no" while 109 (49.5%) said "yes".
- Mean maternal baseline 25(OH)D levels were lower in the "yes" group.
- The values at delivery were nearly equal between the two groups.
- Mean pregnancy 25(OH)D levels were lower in the "yes" group, as were the area under the curve values (indicator of chronic vitamin D status during pregnancy).
- **Of perhaps greatest interest is the finding that mean baby baseline 25(OH)D levels were significantly different between the two groups:**
  - **The "no" group had a mean level of 25.9 and the "yes" group had a mean of 21.9 ($p < 0.05$).**
- These data further support the trend of lower 25(OH)D levels associated with respiratory infection and cold at the earlier ages.

VITAMIN D IN LACTATION

It is widely known that human milk is deficient in vitamin D.

- Dogma of the 20th Century

CLINICAL REPORT

Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

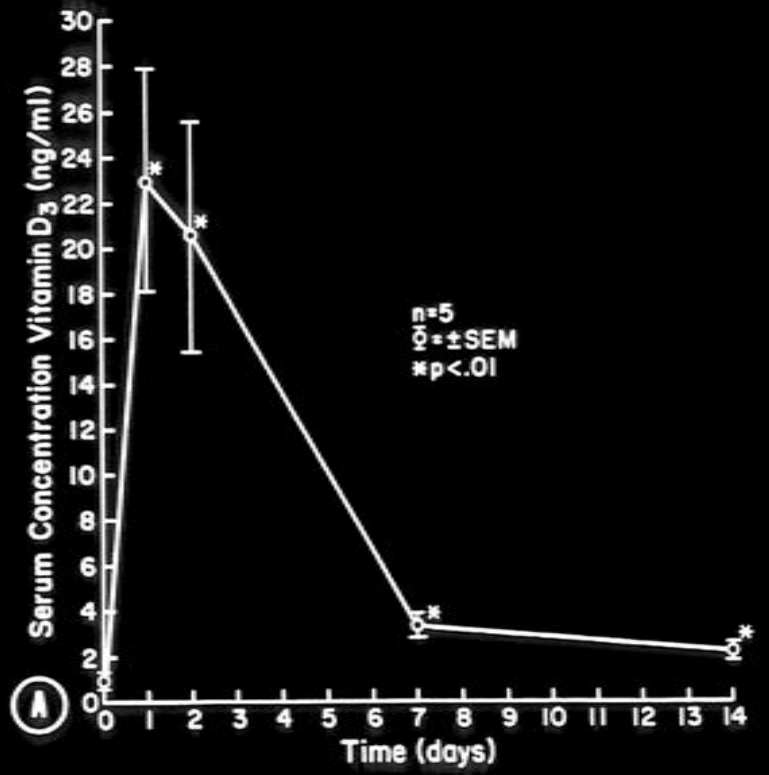
Carol L. Wagner, MD, Frank R. Greer, MD, and the Section on Breastfeeding and Committee on Nutrition

Pediatrics 2008;122:1142–1152

Beyond Current Recommendations

- AAP recommends that all breastfed infants receive vitamin D supplementation starting within the 1st few days after delivery
  - Wagner CL, Greer FR, Section on Breastfeeding, Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008:122:1142–1152.
- Addresses the infant but not mother's status:
  - Could maternal supplementation at higher doses provide adequate levels in breast milk without toxicity to mother?
  - This would effectively treat mother and breastfeeding infant.

Will direct maternal vitamin D supplementation meet the requirements of both the mother and her nursing infant?



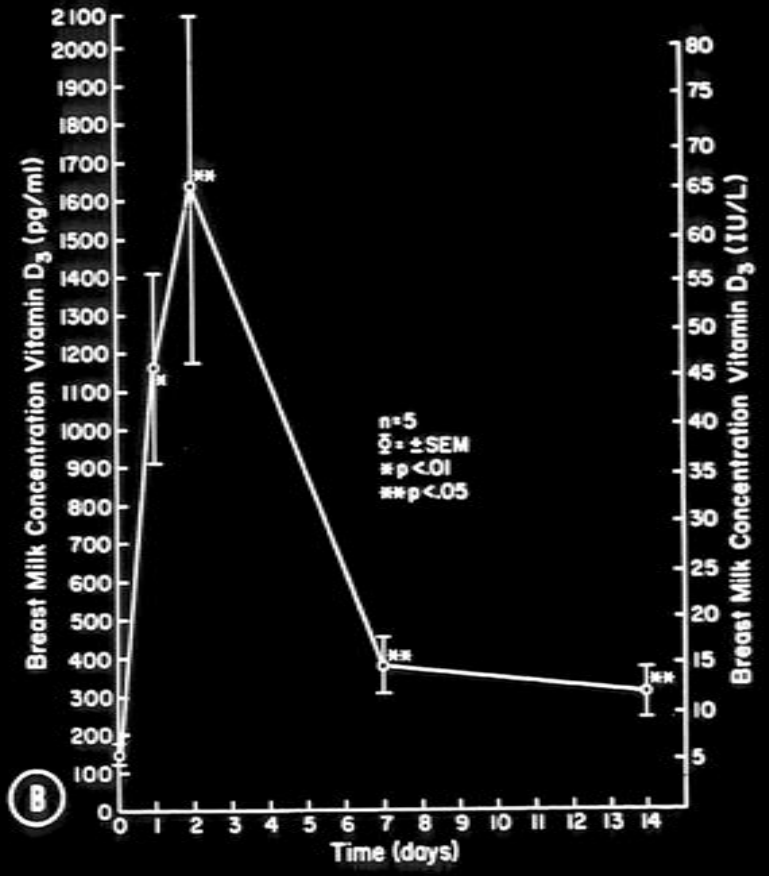
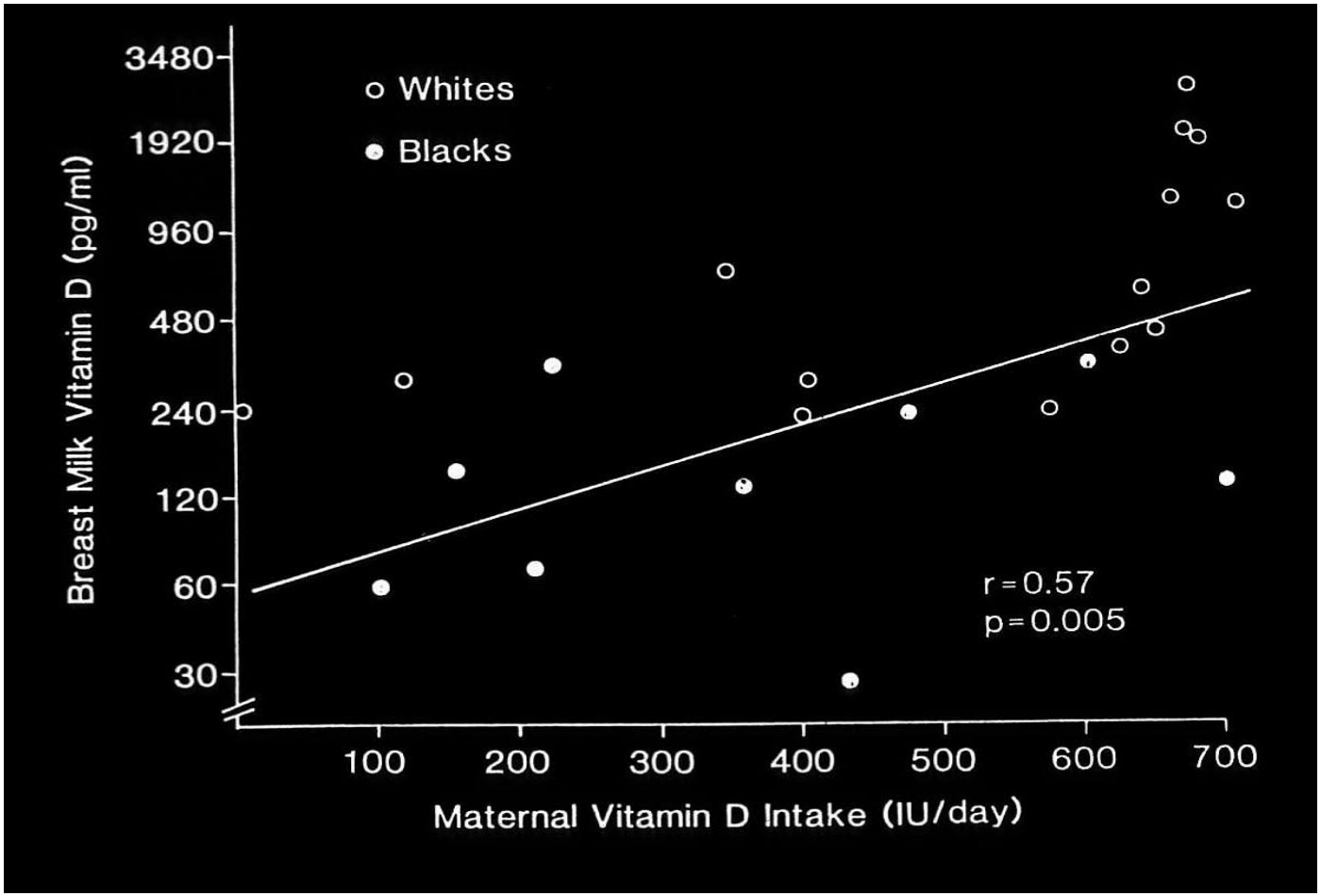


Figure. Serum (**A**) and milk (**B**) concentrations of vitamin D_3 in five white lactating women before and after 1.5 minimal erythemic dose of total body ultraviolet B irradiation.

Cancela, L., LeBoulch, N., and Miravet, L. 1986. Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breastfed infants. *J Endocrinol* 110:43-50.

Cancela et al. (J Endocrinol 1986;110:43-50.)



- Circulating 25(OH)D concentrations in breastfed infants are directly related to the vitamin D content of the mothers' milk

Available evidence indicates that if vitamin D status of the lactating mother is adequate, her breastfeeding infant will maintain a "minimally normal" vitamin D status.

Greer FR, Marshall S. **Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements.** J Pediatr 114 (2) 1989 p:204 -12

Additional Data…

- Data suggest that doses exceeding 1000 IU vitamin D/d (2,000-10,000 IU/d) required to achieve a robust normal concentration of circulating 25(OH)D

  - Vieth et al. Am J Clin Nutr 2001;73:288-94.
  - Heany et al. Am J Clin Nutr 2003;77:204-10.
  - Hollis & Wagner. Am J Clin Nutr 2004.
  - Hollis & Wagner. J Clin Nutr 2004.
  - Wagner, et al. Breastfeeding Med 2006; 2: 59-70

Two Finnish Studies

- Maternal supplements with 1000 IU vitamin D/d resulted in a minimal increases in circulating 25(OH)D concentrations in breastfeeding infants

- Repeated study with 2000 IU vitamin D/d found the vitamin D status of the breastfeeding infants improved significantly

  - Ala-Houhala M. J Pediatr Gastroenterol Nutr 1985;4:220-6.
  - Ala-Houhala et al. Arch Dis Child 1986;61:1159-63.

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.

Main Concerns of High Dose Vitamin D Supplementation

- Toxicity to both mother and her breastfeeding infant
- Or that mother would become toxic but that there would be little transfer to infant
  - Human milk is deficient theory
- There would be a reduction in bone demineralization in mother due to the direct of vitamin D on PTH, with lower levels of calcium to be transferred to the breastfeeding infant.

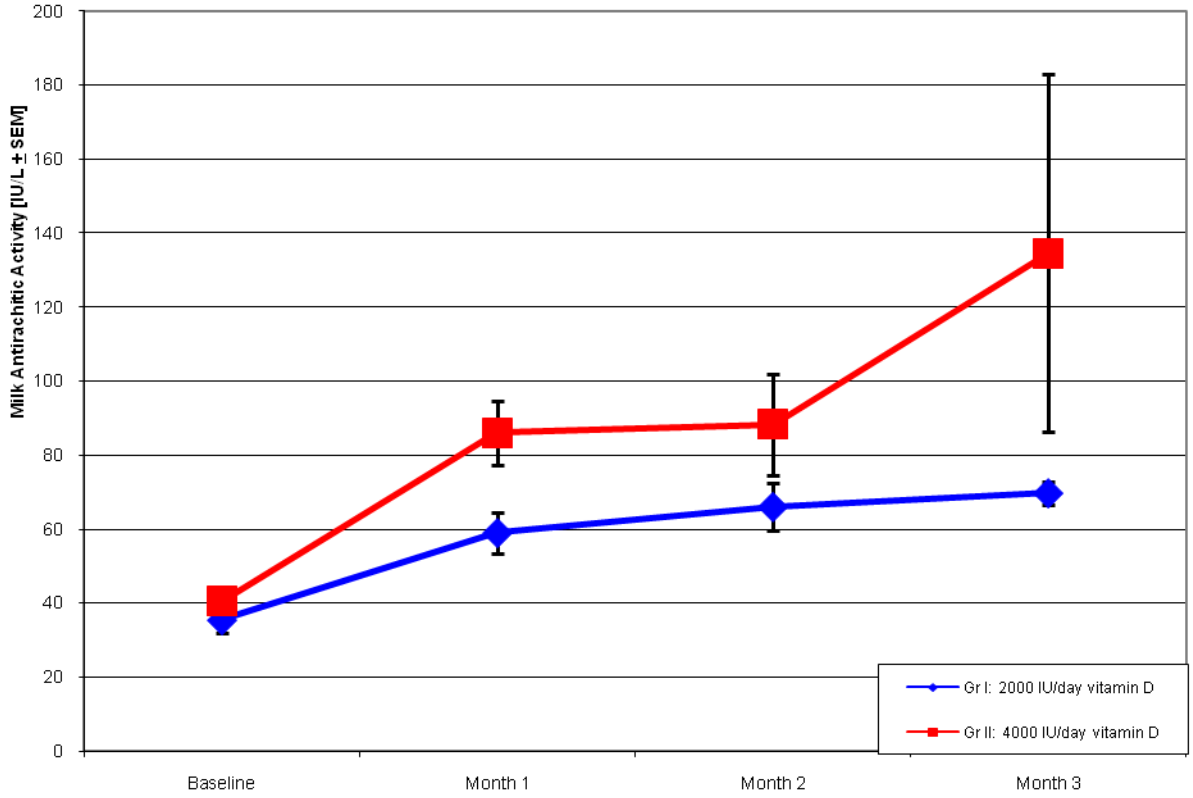
Vitamin D Requirements during Lactation: High-Dose Maternal Supplementation as Therapy to Prevent Hypovitaminosis D in Both Mother and Nursing Infant.

Hollis & Wagner. *Am J Clin Nutrition* 2004; 80S: 1752S-1758S.

Vitamin D Supplementation During Lactation

- 1. To increase the nutritional vitamin D status of the mother
- 2. To improve the vitamin D nutriture of the breastfeeding infant

Longitudinal Assessment of Milk Antirachitic Activity as a Function of Supplementation Regimen in Lactating Women (n=18)



Pilot Study #2: Vitamin D Supplementation Trial of Lactating Mothers and Their Infants

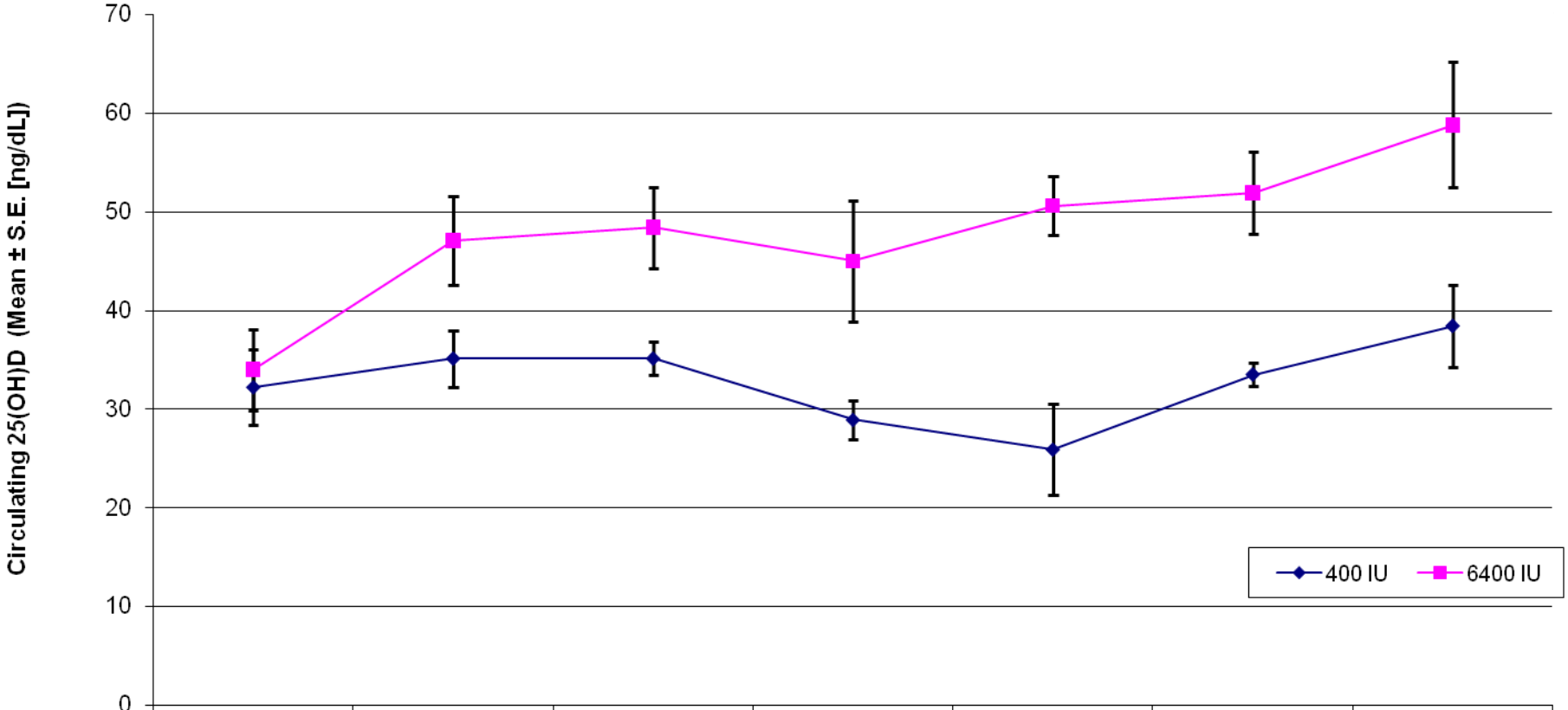
- Mothers were randomized to 1 of 2 treatment groups:
  - 400 vs. 6,400 IU vitamin D_3/day for 6 months starting at 1 month postpartum
- Investigators and study team blinded to assignment group:
  - Infants whose mothers were randomized to 400 IU/d received 300 IU vitamin D_3/day
  - vs. Infants whose mothers were in the 6,400 IU/day group received placebo

Wagner, et al. Breastfeeding Med 2006; 2: 59-70

Results

- There were no adverse events in any mother or infant related to vitamin D
- Compliance with the regimen was higher in the mothers (>90%) than the corresponding infant
  - **Mothers said that they were more often likely to forget to give their infant vitamins than take their own pills**

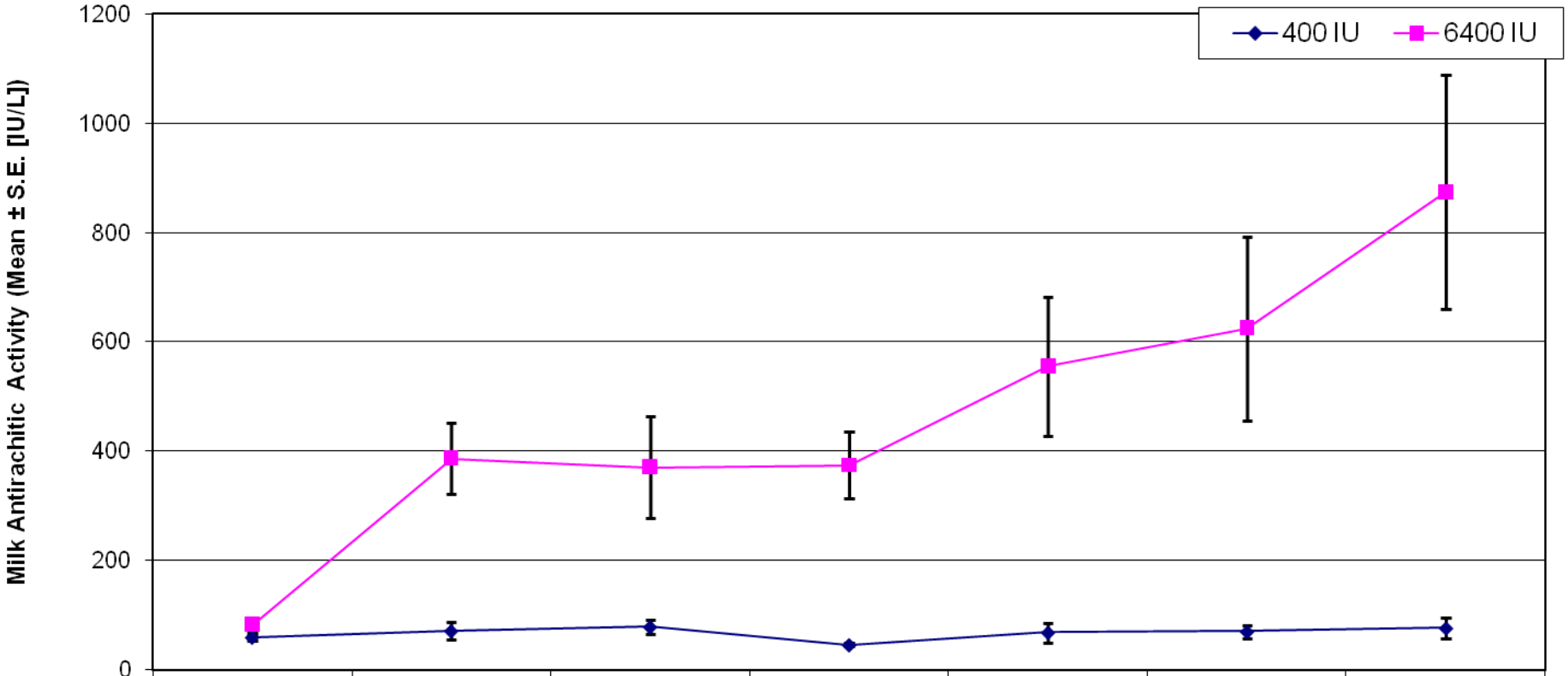
Figure 1. Maternal 25(OH)D Status: 400 IU vs. 6,400 IU Vitamin D_3/day Supplementation Regimen



	1	2	3	4	5	6	7
400 IU	32.2	35.1	35.1	28.9	25.9	33.5	38.4
6400 IU	34	47.1	48.4	45	50.6	51.9	58.8

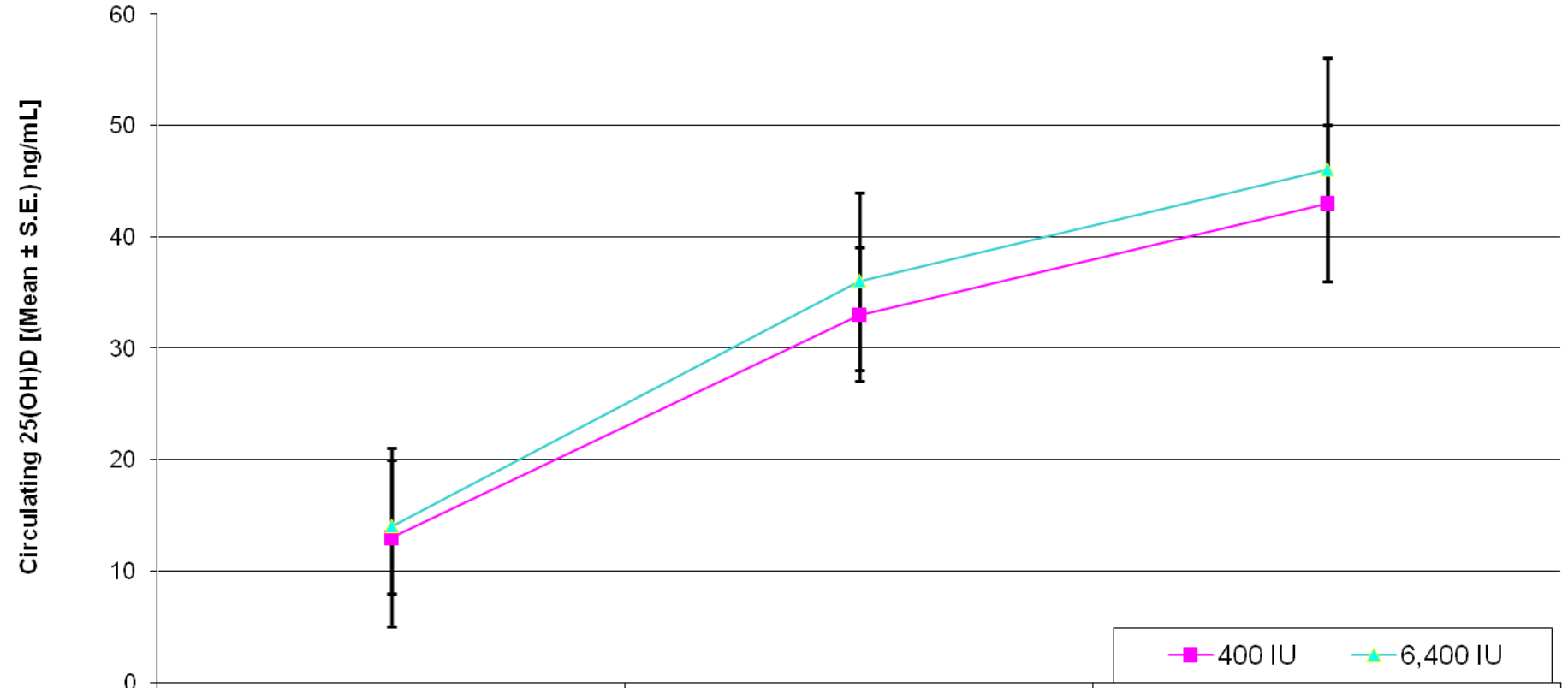
Visit Number

Figure 3. Milk Antirachitic Activity as a Function of Maternal Vitamin D_3 Dose: 400 vs. 6,400 IU/day



	1	2	3	4	5	6	7
400 IU	59.6	71.2	78.6	45.7	68.3	69.9	76.3
6400 IU	82.4	387	370.5	374.4	555.2	624.5	873.5

Figure 4. Infant Circulating 25(OH)D as a Function of Maternal Supplementation (400 vs. 6,400 IU vitamin D_3/day) & Infant Supplementation (300 vs. 0 IU vitamin D_3/day)



	1	4	7
400 IU	13	33	43
6,400 IU	14	36	46

Visit #

Results of 2nd pilot study

- 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.
- We showed both efficacy and effectiveness—
- What we have to show now is safety and effectiveness on a larger scale….

NIH-Sponsored Vitamin D Supplementation Trial of Lactating Women and Their Infants

- Two site study: MUSC and University of Rochester
- Began enrollment November 2006 in Charleston and January 2007 in Rochester
- Mothers recruited by 4-6 weeks postpartum (n=567)
  - Rochester: Lactating Mother/Infant Dyad only (n=189)
  - Charleston: Lactating Mother/Infant Dyad (n=189) & Non-lactating Mothers (n=189)
- Mother and infant dyad followed for 6 mos
  - Following vitamin D status, bone mineralization and safety parameters with visits monthly
- Recently ended 2000 IU arm of study as treatment failed to increase infant levels and a disproportionate number of infants required open label supplementation with 400 IU/day compared with 400 and 6000 IU groups

Effectiveness of Oral Vitamin D Supplementation in Breastfeeding Infants

- Design:
  - As part of larger, ongoing vitamin D supplementation trial of fully lactating women, infants of mothers assigned to the control group received 400 IU vitamin D_3 in one drop per day dosing starting at one month of age.
  - Subjects were enrolled throughout the year.
  - The change in circulating 25(OH)D levels in those infants was measured.
  - As part of our data safety and monitoring process, levels of those infants randomized to the control group in a blinded fashion were analyzed to determine effectiveness of the daily one drop/day vitamin D dosing method.
  - Infant 25(OH)D levels (mean $\pm$ S.D.) were measured by radioimmunoassay at Visits 1 (~1 month of age; baseline), 4 and 7.
  - Data were analyzed by Paired Student's t-test and repeated measures ANOVA; significance was set at 0.05 *a priori*.

Wagner CL, et al, 2010 J Int Endocrin

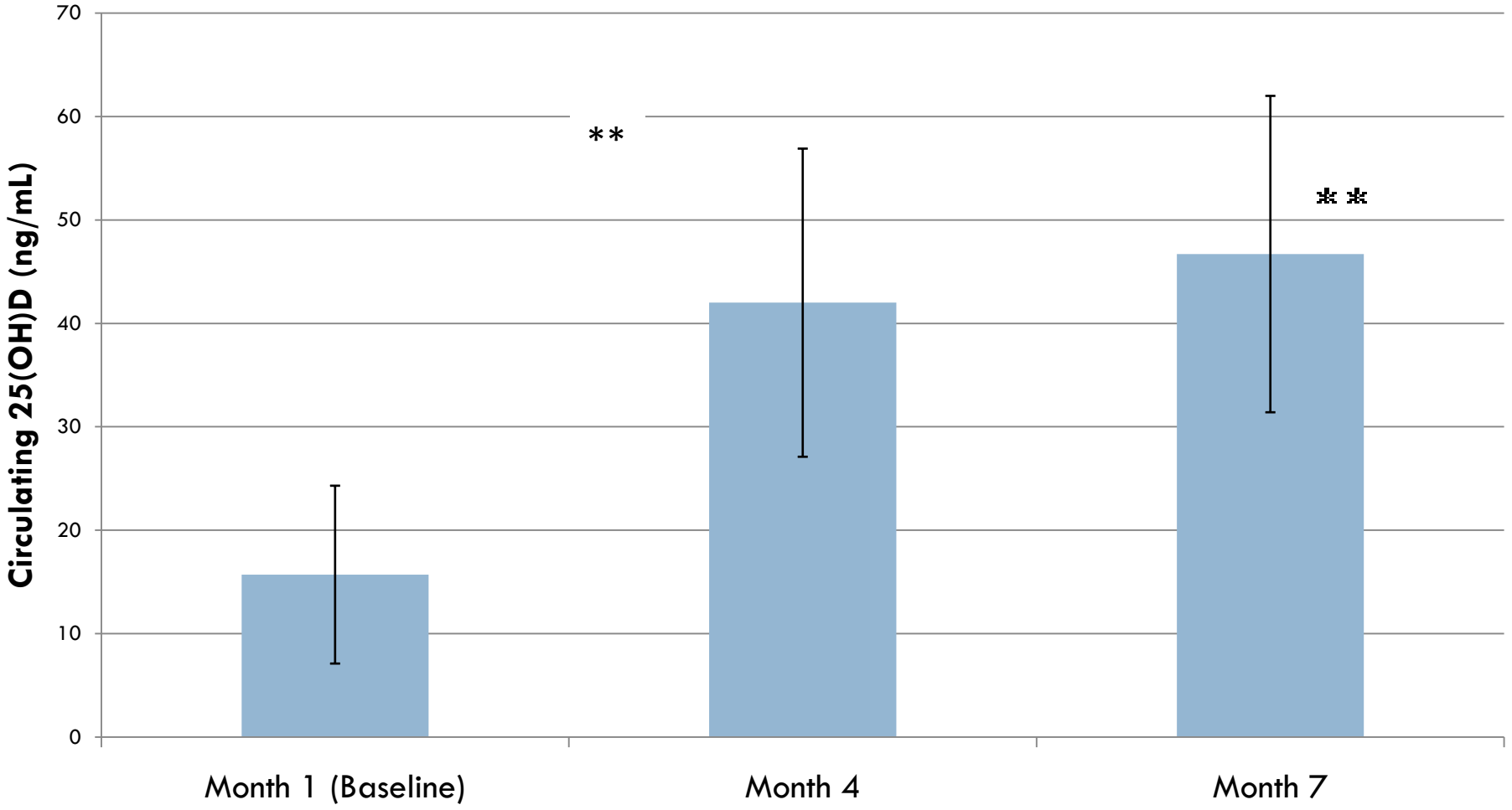
Results

- 54 mothers and their infants were enrolled in the study and randomized to the control group in a blinded fashion; 33 have completed the study through visit 7.
- The mean ± S.D. 25(OH)D at one month (baseline) for the infants was:
  - 16.0 ± 9.3 ng/mL (range 1.0-40.8; n=33)
  - 24 (72.7%) had baseline levels <20 ng/mL (consistent with deficiency)
- Mean levels increased to 43.6 ± 14.1 (range 18.2-69.7) at 4 months and remained relatively unchanged at month 7: 42.5 ± 12.1 ng/mL (range 18.9-67.2).
  - Change in values between 1 and 4 months, 1 and 7 months was statistically significant ($p \leq 0.0001$).
- As predicted, there were no statistically significant differences between months 4 and 7 ($p=0.66$).
- Even with changes in season, the results remained significant. On an IU/kg basis, at visit 1, the infants were receiving 88.9 ± 10.5 IU/kg; at visit 4, they were receiving 59.7 ± 6.6 IU/kg; and at visit 7, they were receiving 50.5 ± 6.0 IU/kg ($p<0.0001$).
- Despite the decrease in dose on a per kilogram basis, the infant mean circulating 25(OH)D levels were not significantly different between visit 4 and 7.

Infant Weight, Vitamin D Status and Dosage per Body Weight

Variable	Visit 1 (n=54)	Visit 4 (n=27)	Visit 7 (n=22)
Infant wt (mean ± S.D.)	4.6 ± 0.44 kg	6.8 ± 0.79 kg	8.0 ± 1.03 kg
Total circulating 25(OH)D [ng/mL)	16.3 ± 8.9	43.3 ± 13.7	42.2 ± 12.3
IU Vitamin D/body wt (kg)	87.3 ± 8.3	59.5 ± 7.0	50.8 ± 6.2

Total Infant Circulating 25(OH)D (ng/mL)



**p<0.0001

Conclusions

- Oral vitamin D_3 supplementation as an oil emulsion (400 IU/drop) was associated with significant and sustained increases in circulating 25(OH)D from baseline in fully breastfeeding infants through 7 months of age.

For pregnant women

- 4,000 IU vitamin D/day was found to be safe and effective in raising maternal circulating 25(OH)D levels
  - Associated with lower risk of preterm labor/birth and overall infections during pregnancy
- Issues remain about nonadherence or noncompliance:
  - Daily vs. weekly administration

For Lactating Women

- Maternal circulating 25(OH)D levels could be checked—
  - if levels >60 ng/mL, there is **likely** no need for supplementation of breastfeeding infant as maternal milk will have good levels.
  - HOWEVER, DON'T ASSUME SUFFICIENCY: you would have to check both maternal and infant levels to assure sufficiency.
- Supplement lactating mother with high dose vitamin D and treat both mother and infant:
  - **Unproven/experimental** at this time
- Achieve circulating 25(OH)D levels of at least 30 ng/mL in all your patients, and don't forget yourself!
- When in doubt, check a level…

For the breastfeeding infant

- Supplement breastfeeding infant with 400 IU vitamin D_3/day to ensure adequate intake
  - Bio-D-Mulsion (Biotics Research Corp)
  - Just D (Sunlight Vitamins)
  - D-drops and gel caps (400 and 2,000 IU; Carlson Labs)
- Combination fed infants should receive vitamin D supplementation as well
- Exclusively formula-fed infants do not require supplementation is they are taking in greater than 1 liter formula per day
- Ongoing research will assess the safety and effectiveness of maternal supplementation with the premise that making mother replete in vitamin D will allow adequate transfer of vitamin D in her milk and thus adequate levels in her breastfeeding baby

Indication for Measurement

- When nutritional deficiency of vitamin D is suspected
  - Intestinal malabsorption syndromes
  - Patients on chronic anti-epileptic drugs
  - Limited exposure to the sun: the average American in 1989 spent 93% of their time indoors—imagine the stats in 2009!
    - This happens even in San Diego, especially for those who work indoors such as a medical center!
  - Limited intakes of oral vitamin D supplements
  - Aged, homebound patients
  - Darkly pigmented individuals
  - Thorough use of sunscreen

Conclusions

- We are in the midst of a **vitamin D deficiency epidemic.**
- There are many reasons why, not the least of which is that we made too many assumptions about vitamin D.
- It is quite likely that chronic nutritional vitamin D deficiency puts all of us at risk for developing debilitating, long latency chronic diseases such as insulin resistance/diabetes, cardiovascular disease, cancer and autoimmune diseases.
- Society will need to understand the role that vitamin D plays in health—beyond bones and mandate policy changes at the national level.
  - That mechanism of change begins with <u>you</u>.


The children…they are our future.
29 6:54 PM

Thank you