Vitamin D During Pregnancy & Lactation

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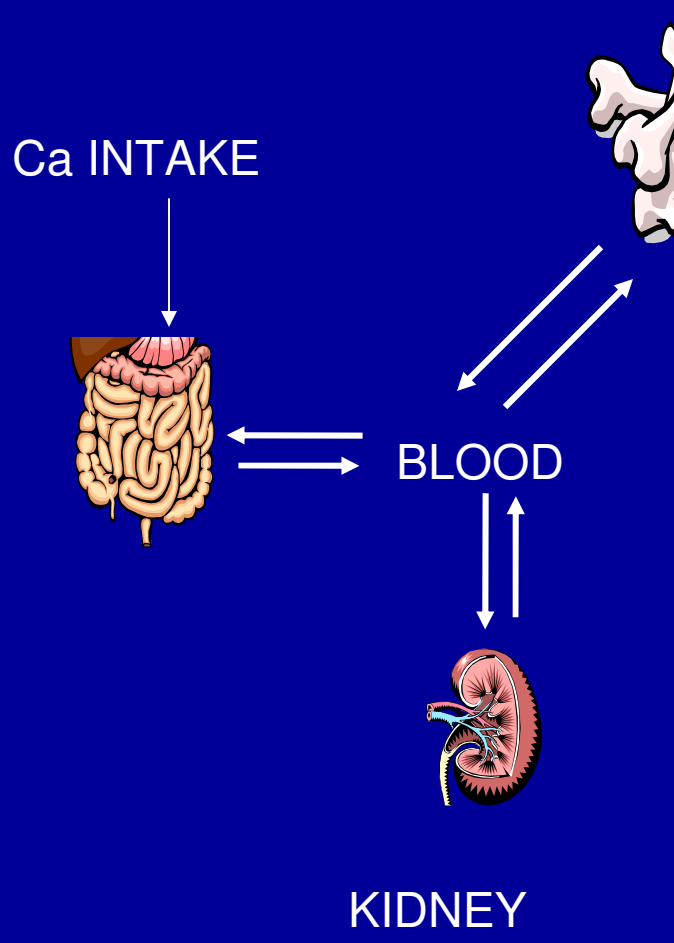
Calcium Demands

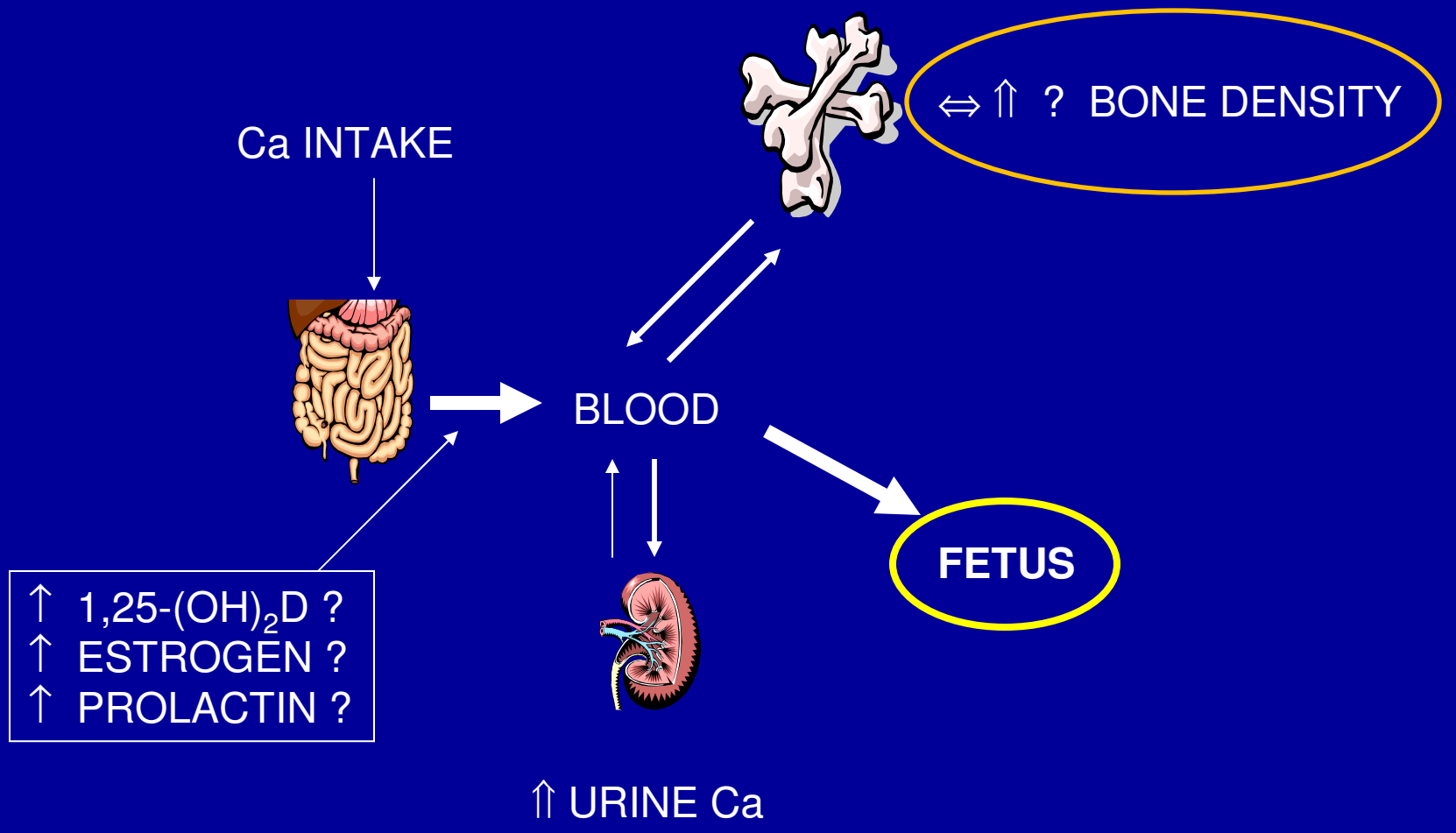


Most studies of vitamin D requirements during pregnancy & lactation use calcium and bone outcomes.

Numerous hormones are involved in calcium homeostasis:

- 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$)
- parathyroid hormone (PTH)

Meeting Fetal Calcium Demands



Maternal Changes in Bone During Pregnancy

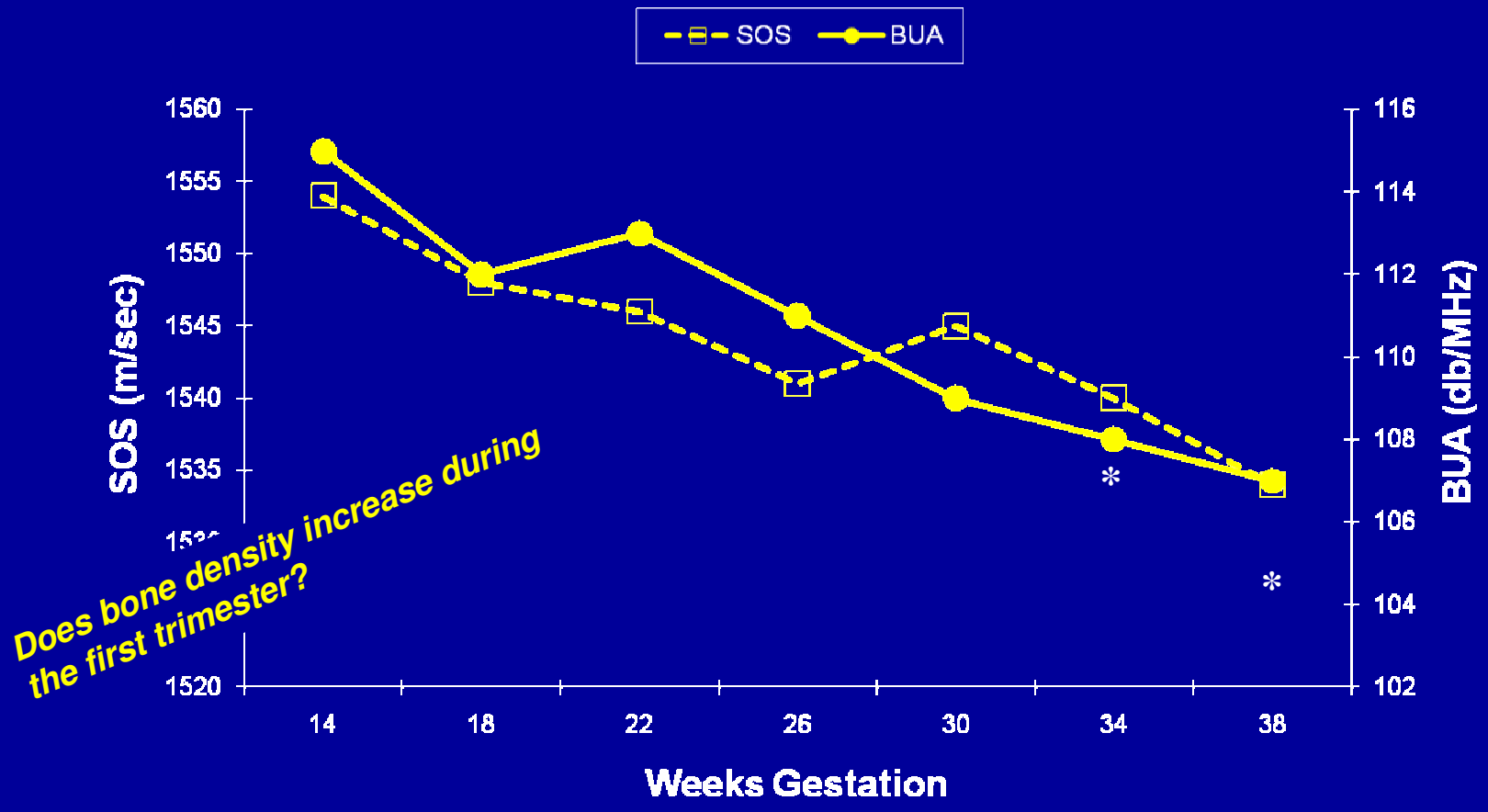
Findings in *healthy* populations:

Maternal Findings	**# of Longitudinal Studies**
Decrease in bone density	**6 studies** **2-4% loss**
Increase in bone density	**1 study**
No change in bone density	**4 studies**

Difficulties with previous studies:

- Final bone measurements are made up to 6 weeks postpartum – a time when lactation-induced bone changes have already occurred.
- Small sample sizes.
- Few studies have measurements throughout pregnancy due to radiation exposure of DXA.

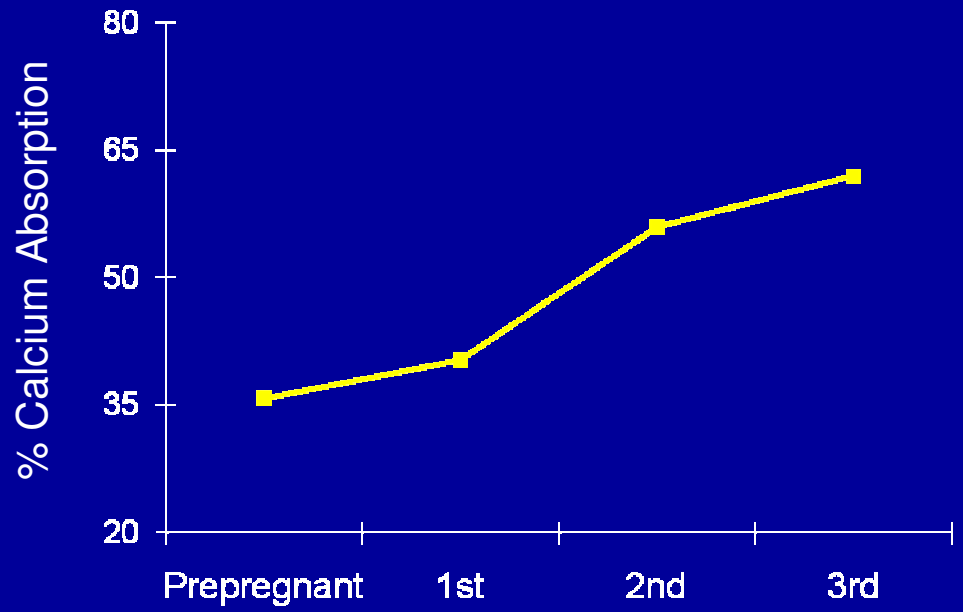
Maternal Changes in Bone Measured by Ultrasound



* p<0.05 compared to 14 weeks gestation

Gambacciani, 1995

Calcium Absorption During Pregnancy



Ritchie et al., 1998

Intestinal calcium transport genes are up-regulated by estrogens during pregnancy and are independent of vitamin D.

Van Cromphaut et al., 2003

Meeting Fetal Calcium Demands

During vitamin D deficiency:

25-OHD	$\Downarrow$
PTH	$\Uparrow$
1,25-$(OH)_2$D	$\Uparrow$

After extended period of time:

25-OHD	$\Downarrow\Downarrow$
PTH	$\Uparrow\Uparrow$
1,25-$(OH)_2$D	$\Downarrow$

Long-term vitamin D deficiency will result in decreased maternal 1,25-$(OH)_2$D and increased PTH. This is especially true with low Ca or high P intakes.

Meeting Fetal Calcium Demands

At adequate levels of vitamin D, the calcium demands of the mother and fetus are met through increased intestinal calcium absorption.

Severe vitamin D deficiency with secondary hyperparathyroidism during pregnancy leads to abnormal calcium homeostasis in the neonate.

Vitamin D and Neonatal Calcium

Studies included in review:

Observational Studies

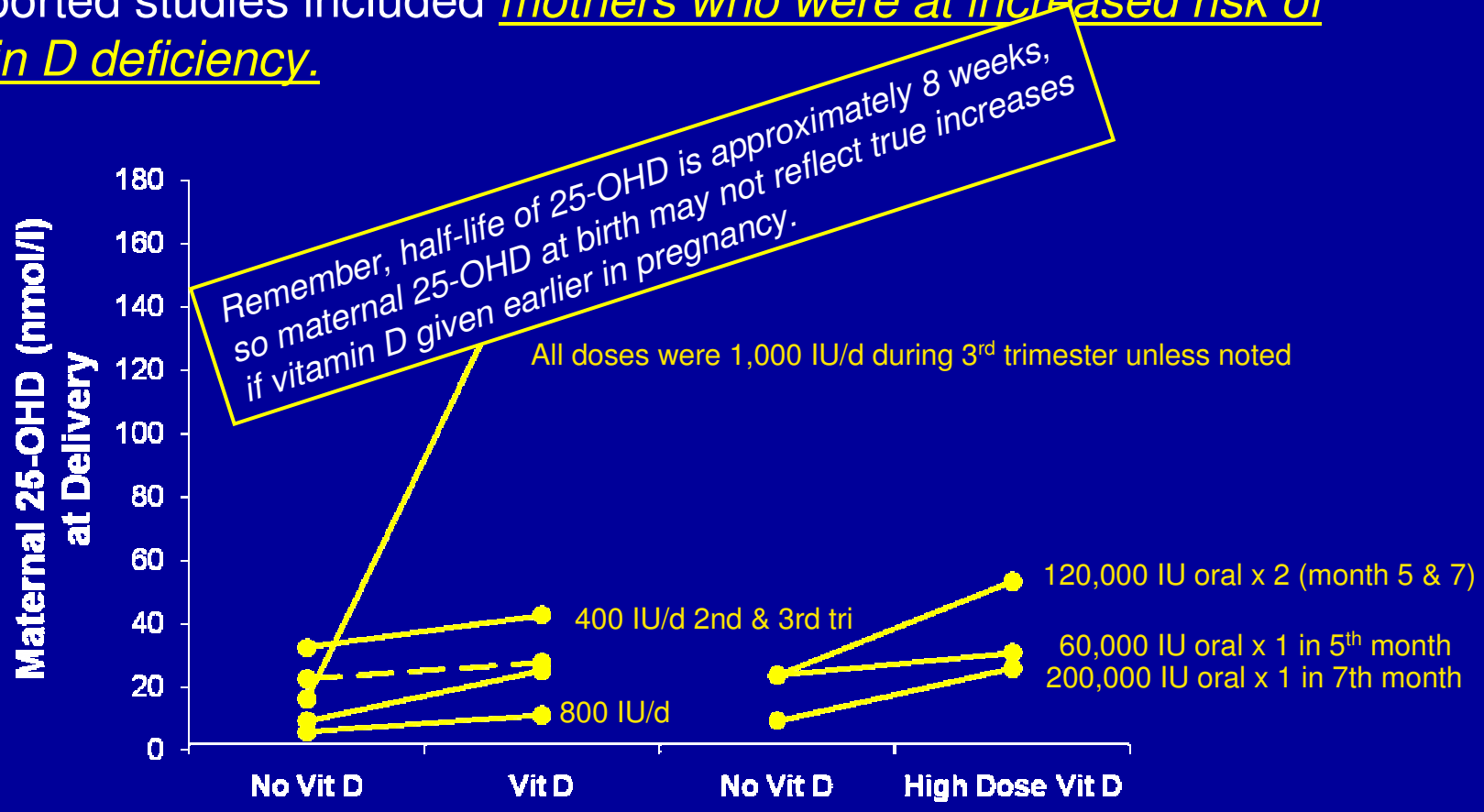
Paunier et al., 1978	N = 32
Datta et al., 2002	N = 80

Trials (clinics or subjects randomized or assigned)

Cockburn et al., 1980	N = 1,139
Brooke et al., 1980 (1981) (also Maxwell et al., 1981)	N = 126 (117)
Marya et al., 1981	N = 120
Delvin et al., 1986	N = 34
Mallet at al., 1986	N = 68
Marya et al., 1988	N = 200
Sahu et al., 2009	N = 84

Vitamin D and Neonatal Calcium

All reported studies included *mothers who were at increased risk of vitamin D deficiency.*

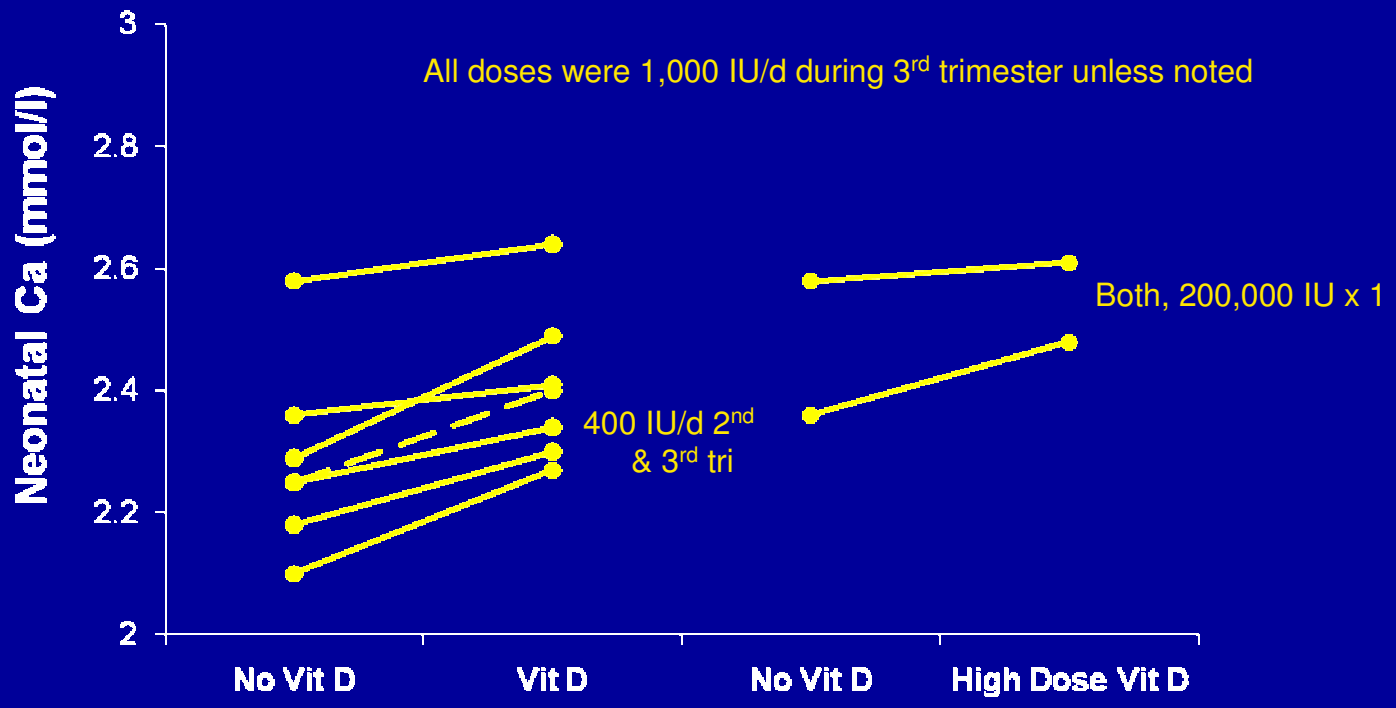


Data from studies that had mean maternal 25-OHD at delivery. Lines connect means from same study.
Study with the dashed line is an observational study (500-1500 IU/d of Vit D)

Maternal vitamin D supplementation increases cord 25-OHD concentrations (which are typically 50% of maternal concentrations)

Vitamin D and Neonatal Calcium

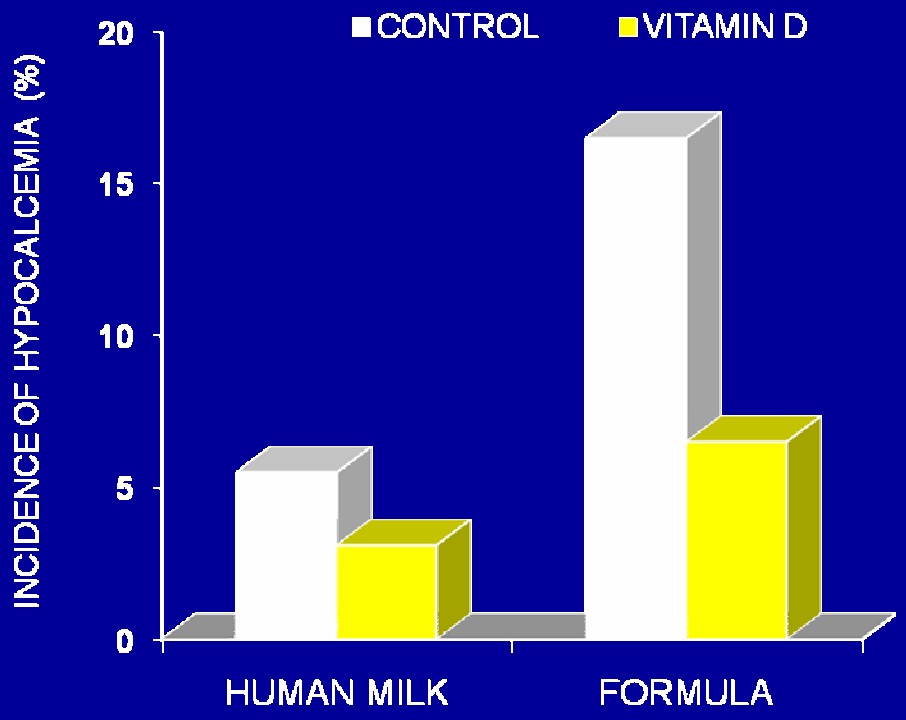
- Neonatal serum calcium concentrations change significantly over the first 24 hours after birth.
- Most studies find higher calcium concentrations among infants whose *high risk mothers* received vitamin D.



Data from trials that had mean neonatal calcium concentrations during the first week of life.
Dashed line is an observational study (500-1500 IU/d in Vit D).

Vitamin D and Neonatal Calcium

Neonatal calcium is also influenced by other factors, including dietary phosphorus intake.



Subjects:
Asian-Indian women residing in Scotland

Two Clinics:
1. Control – no vitamin D (N=633)
2. Vitamin D – 400 IU/d from 12th week gestation (N=506)

Cockburn et al. (1980)

Vitamin D and Maternal & Fetal Weight Gain

It has been speculated that severe vitamin D may be related to poor maternal weight gain or fetal growth.

Marya 1988

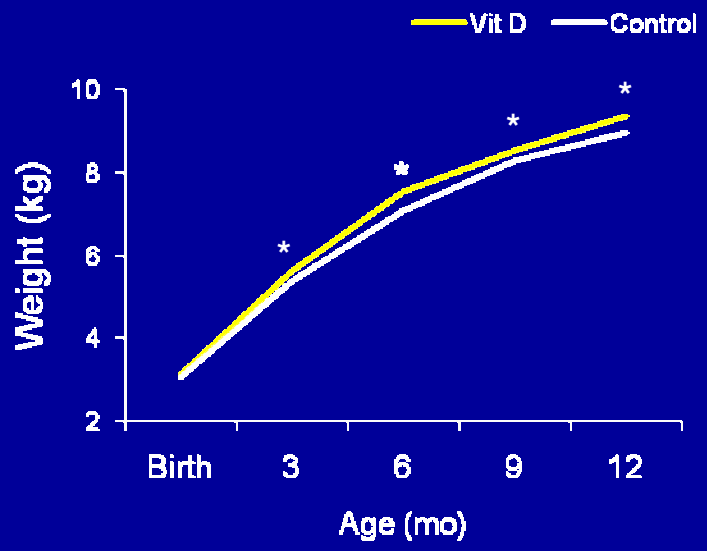
Number of Studies (total participants)	Maternal Weight Gain During Pregnancy	Birthweight
Not Reporting	**6** (1465)	**3** (1281)
Finding an Effect	**1** (126)	**2** (320)
Finding No Effect	**1** (200)	**3** (190)

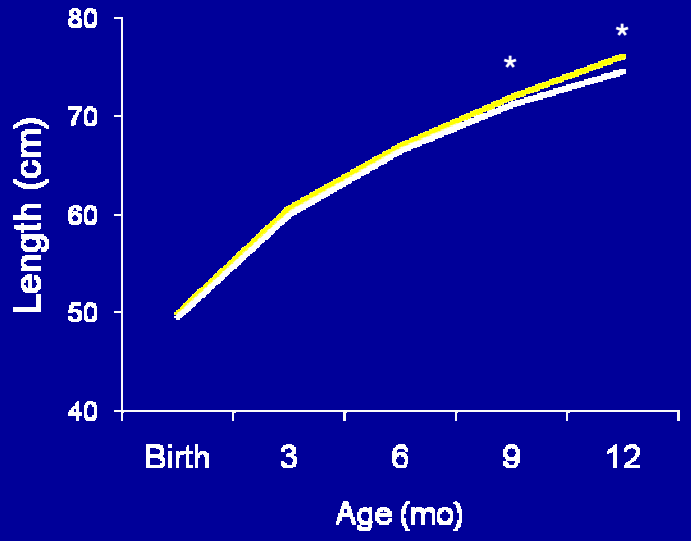
…but results are not consistent.

Vitamin D during Pregnancy and Postnatal Growth of the Child

A follow-up study of infants whose mothers participated in a vitamin D supplementation study found no difference in birth weight or length, but greater weight and length later in infancy.

Brooke et al., 1981

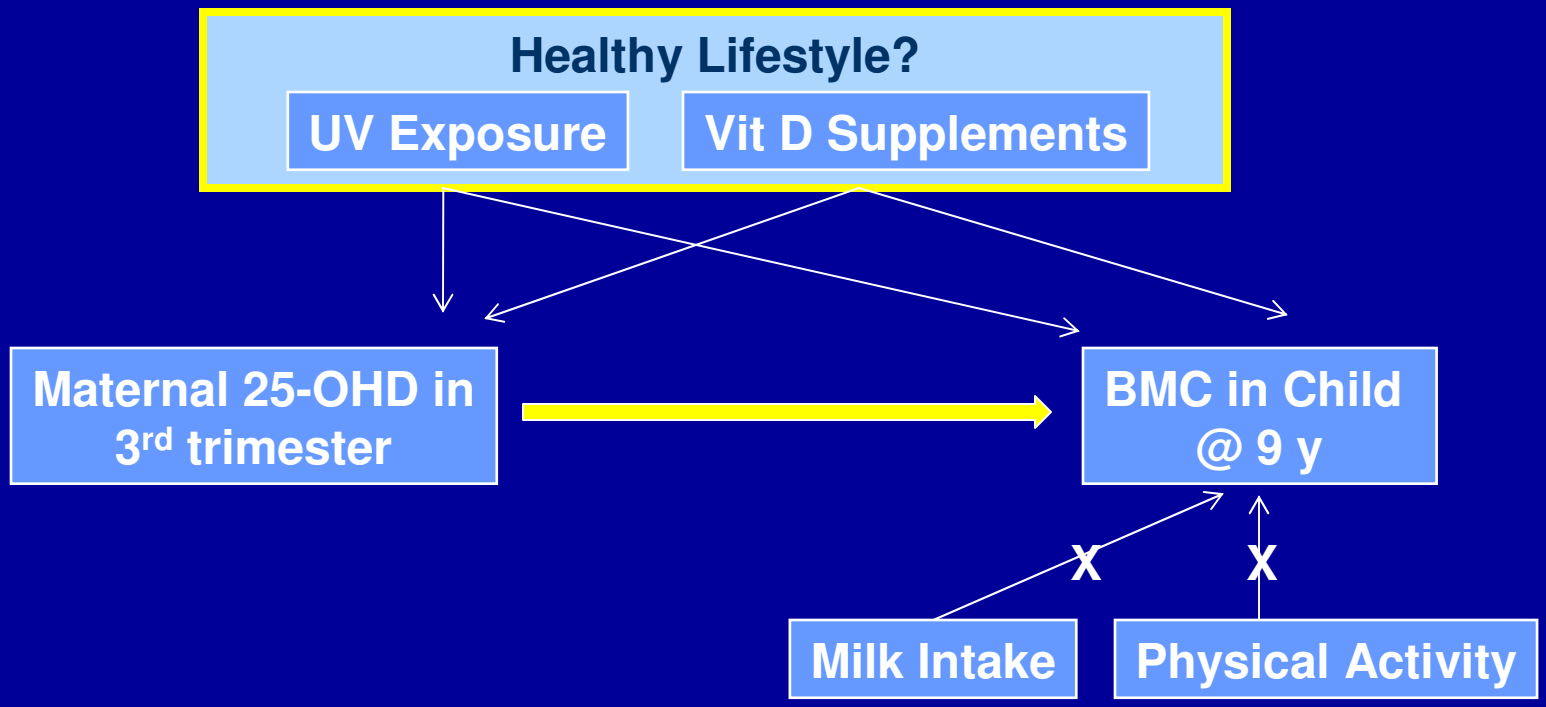




Vitamin D during Pregnancy and Later Bone Mass of the Child

- Longitudinal study of **198** children aged 9 years in Southhampton, UK
- Mothers had 25-OHD concentrations measured in 3rd trimester

Javaid et al., 2006



Vitamin D during Pregnancy and Later Bone Mass of the Child

Subjects & Methods:

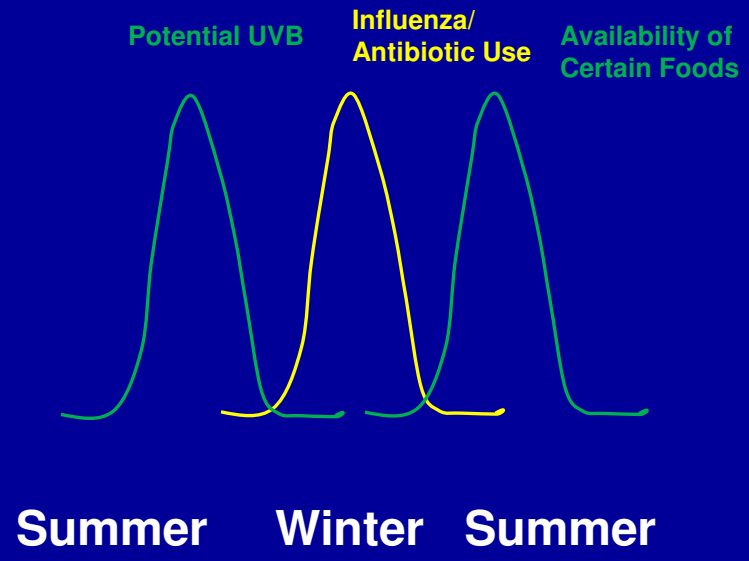
- Longitudinal study of 6,995 children aged 9 years: Avon Longitudinal Study of Parents and Children (ALSPAC, UK)
- **355** mothers had 25-OHD concentrations measured in 3rd trimester
- UVB exposure estimated from meteorological records (correlated with maternal 25-OHD)

Results:

- Estimated UVB exposure in 3rd trimester correlated with:
  - birth length
  - height, weight, BMC and lean mass at age 9 years
- Estimated UVB exposure associated with bone area even controlling for height and lean mass.
- "…***examined childhood bone mass in relation to maternal 25-OHD in this subgroup, but there was little evidence of an association.***"

Sayers & Tobias, 2009

Vitamin D during Pregnancy and Later Bone Mass of the Child



Is there some other common factor that could explain differences in growth later in life?

Vitamin D during Pregnancy and Later Asthma Risk

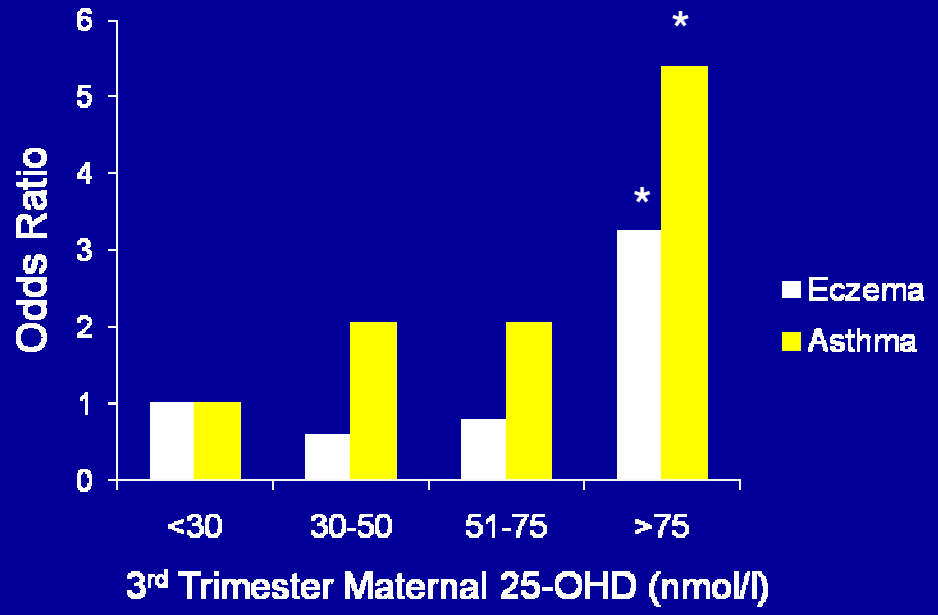
Vitamin D has a number of immunological effects and may play a role in preventing autoimmune diseases.

Some observational studies, but not all, have found an association between maternal vitamin D during pregnancy and later risk of wheeze or asthma in the children.

- Relationship between maternal dietary vitamin D and asthma risk later in childhood (N=1,669): *but*, no relationship with vitamin D from supplements? (Erkkola et al. 2009)
- Relationship between maternal vitamin D intake and asthma risk was not modified by maternal BMI (N=1,194): *but*, mothers with high BMI should have lower serum 25-OHD concentrations? (Camargo et al., 2007)

Vitamin D during Pregnancy and Later Asthma Risk

- Relationship between wheeze at age 5 y and maternal vitamin D intake in pregnancy (N=1,212): *but*, maternal vitamin D intake was not associated with asthma or spirometry, *and* other nutrients also were important (Zn, vit E) (Devereux et al., 2007)
- A study that measured maternal serum 25-OHD found high maternal 25-OHD during pregnancy was associated with ***increased*** risk of visible eczema and asthma at 9 years (data below from Gale et al., 2008)



Potential Risks Associated with Vitamin D Supplementation during Pregnancy

- During the 1960's large vessel calcification associated with infantile hypercalemia was observed in the UK – originally thought to be due to vitamin D fortification.
- Studies in rats supplemented with *high* vitamin D doses during pregnancy have shown their offspring to have a slowing of cardiac development (Norman et al., 2002).
- Studies conducted in 6-week old piglets whose mothers were randomized to either low or high vitamin D supplementation during pregnancy found adverse effects on vasculature: 25-OHD in the high group = 30 ng/ml (Toda et al., 1985)
- Maternal 25-OHD concentrations (3rd trimester) were not associated with measures of cardiac function in offspring at age 9 years (Gale et al., 2008)

Vitamin D During Pregnancy
- Summary -

- Increased intestinal calcium absorption during pregnancy (independent of vitamin D status) meets fetal calcium demands.
- In severe maternal vitamin D deficiency, PTH is increased & 1,25-$(OH)_2D$ is decreased - osteomalacia may occur.
- Vitamin D supplementation among pregnant women at high risk of vitamin D deficiency show:
  - an improved maternal & neonatal vitamin D status
  - an improved neonatal handling of calcium

Vitamin D During Pregnancy
- Summary -

The following effects of vitamin D during pregnancy are conflicting and inconclusive:

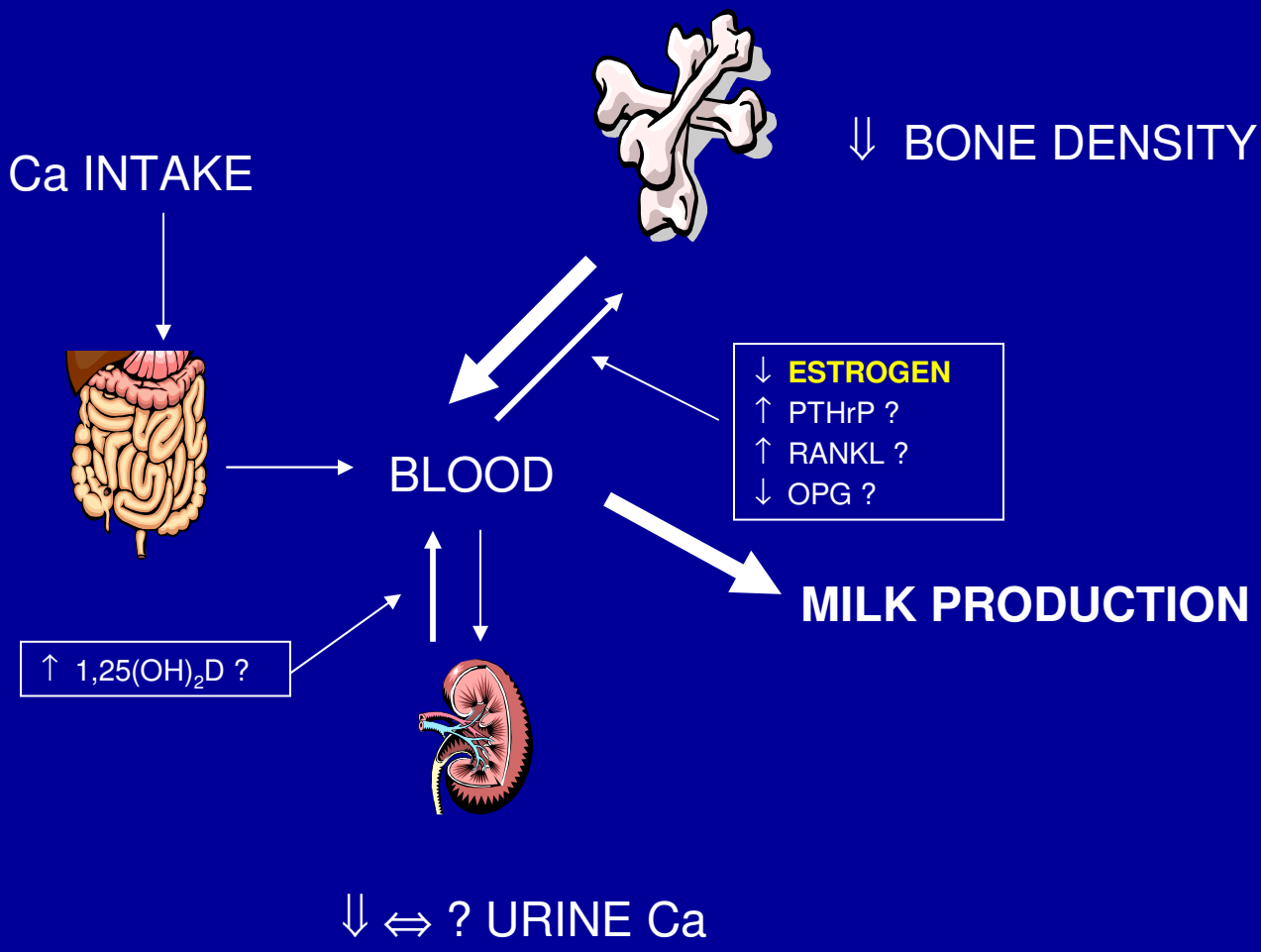
- maternal weight gain
- fetal growth and bone mineralization
- bone health and asthma risk later in life
- adverse effects of high doses of vitamin D

Vitamin D Requirements During Lactation

Requirements based on the mother or infant?

- **Mother** – no evidence to suggest that requirements are greater than during non-lactating state
- **Infant**
  - Primary source of vitamin D for the infant:
    - <8 weeks of age: placental transfer
    - >8 weeks of age: sunshine exposure
  - Human milk contains negligible amounts of vitamin D
    - Can mother be supplemented so that milk will contain sufficient amounts?

Meeting Demands for Milk Production



Meeting Demands for Milk Production

Kinetic Studies

Net flow of Ca from bone	2.72 mg/kg/d
Conserved through reduced renal excretion	0.68 mg/kg/d
Ca entering the body pool:	3.40 mg/kg/d
Ca loss in milk (approx)	3.10 mg/kg/d

Bone is lost during lactation.

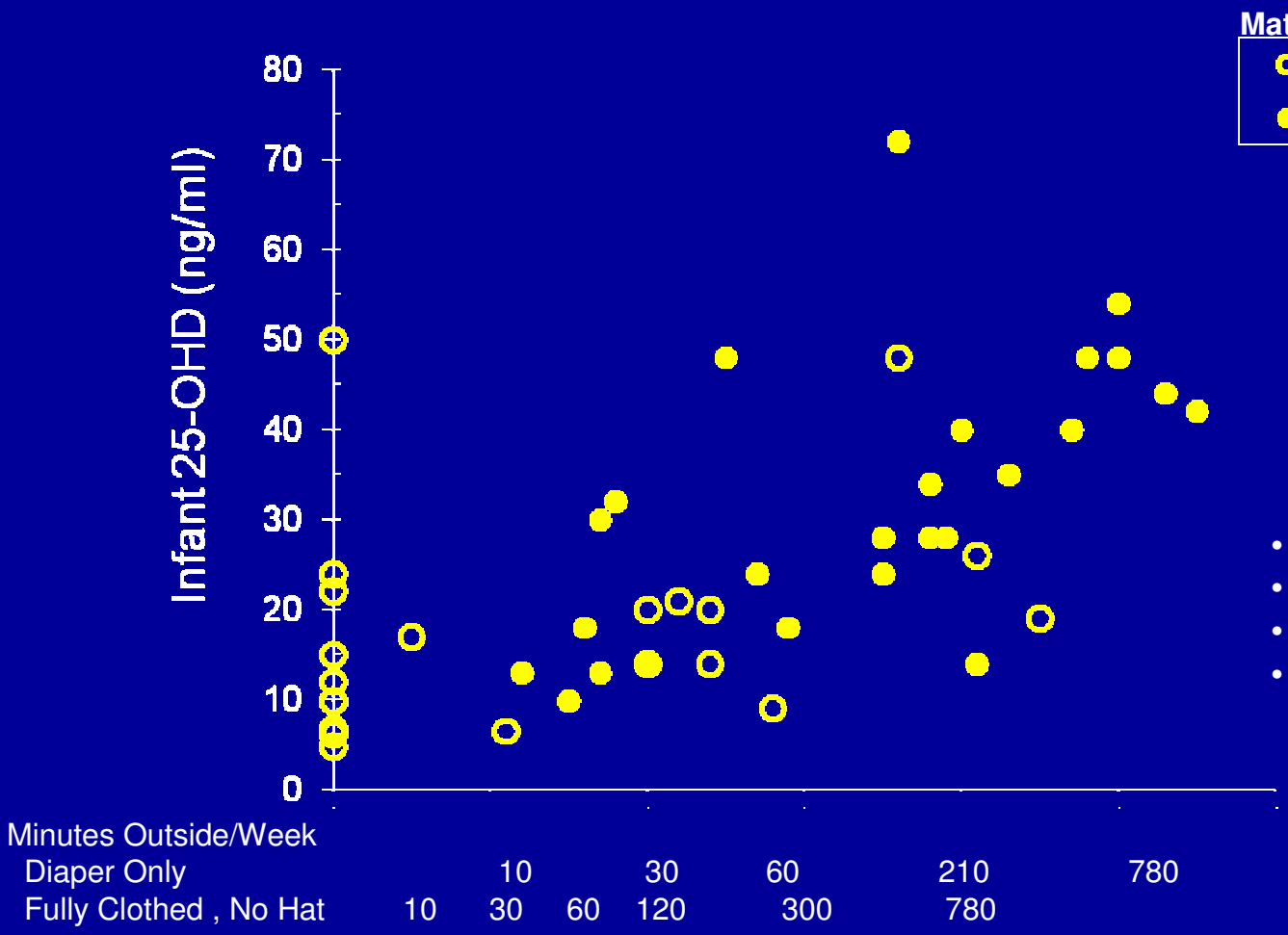
- Numerous studies have shown that the bone loss is related to low estrogen levels.
- Increasing calcium intake in vitamin D sufficient mothers does not prevent maternal bone loss.
- There is no reason to believe that increasing vitamin D intake above those required in non-lactating women would prevent maternal bone loss.

Long-term Consequences of Pregnancy & Lactation on Maternal Bone Health

Studies find that women with high parity (with or without breast-feeding) have reduced hip fracture risk:

- Case-control study of 1,328 hip fractures & 3,312 controls found hip fracture risk was reduced by 10% per child (Michaelsson et al., 2001)
- Longitudinal study of 10,000 women found decreased hip fracture in parous vs. nulliparous women. However, there was no difference in BMD by DXA in parous vs. nulliparous women (Hillier et al., 2003)
- Cross-sectional study of older women found ncreased bone size with higher parity that could explain reduced fracture risk (Specker et al., 2005)

Vitamin D in the Breast-Fed Infant



- Latitude 39' 09° N
- Infants <6 months of age
- Exclusively breast-fed
- Never received vitamins

Sunshine exposure was the most significant predictor of infant 25-OHD concentrations.

Specker et al., 1985

Vitamin D in the Breast-Fed Infant

Regression analyses were performed and a conservative estimate* of the amount of time outside to maintain infant serum 25-OHD concentrations above 11 ng/ml was obtained:

30 minutes/week with a diaper only

or

2 hours/week fully clothed with no hat

Note: sunscreen was not in use at the time this study was completed.

* Feiller's theorem was used to estimate the upper 95% confidence limit of where regression line intersects at y = 11 ng/ml.

Specker et al., 1985

Vitamin D in the Breast-Fed Infant

- Longitudinally study of 25 infants from birth to 1 year of age
- Exclusively breast-fed & no vitamins during the first 6 months
- Infants born in summer and winter had opposite, cyclical changes in UVB exposure that took into account surface area of the body that was exposed.
- Serum 25-OHD concentrations in these infants over the first year of life paralleled the changes seen in UVB exposure.

Specker et al., 1987

Milk Vitamin D Concentrations

- Total vitamin D activity (D + 25OHD) measured in mother's milk:
  - Black mothers - 34 IU/L
  - White mothers - 64 IU/L
- Milk vitamin D was correlated to maternal vitamin D intake (0-700 IU/L; r=0.57).

Conclusion: Total vitamin D in human milk is low.

Specker et al., 1985

Milk Vitamin D Concentrations

49 Finnish mother-infant pairs studied at delivery and 8 & 15 weeks:

Infants supplemented with 400 IU/d had similar increases in serum 25-OHD concentrations as infants whose mothers were supplemented with 2,000 IU/d.

Ala-Houhala et al., 1986

Milk Vitamin D Concentrations

Women were supplemented with either:

- 400 IU/d vitamin D_3 & their infants with 300 IU/d of vitamin D_3 (N=10)
- 6,400 IU/d vitamin D_3 (N=9)

Women with 6,400 IU/d had milk concentrations of approximately 800 IU/L at the end of the 7 month lactation.

Whether the women or infants who are supplemented with the higher dose of vitamin D have differences in ***functional outcomes*** compared to the women and infants receiving the lower doses is currently being studied.

Wagner et al., 2006

Vitamin D During Lactation
- Summary -

- There is no evidence to suggest that requirements for the mother are greater than during non-lactating state.
- Primary source of vitamin D for the infant is sunshine exposure. If sunshine exposure is limited, the infant must depend on exogenous sources for vitamin D.
- Milk vitamin D levels are low.
- There is evidence that increasing mothers' vitamin D intake (>=2,000 IU/day) may increase the infants' serum 25-OHD concentrations to levels comparable with directly supplementing the infant with 400 IU/day.

Vitamin D During Lactation
- Summary -

- It is not clear what the functional indicators for the lactating mother or infant should be.
- Once the functional indicators are determined, the level of serum 25-OHD to optimize these indicators can be determined.
- The dietary intakes to achieve this level of serum 25-OHD concentrations could be recommended.

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