EVERYTHING YOU NEED TO KNOW ABOUT
VITAMIN D & PREGNANCY

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VITAMIN D

"At no point in human nutrition is it more critical to ensure adequate nutrient intake than during the state of pregnancy."
- Bruce Hollis, PhD

OBJECTIVES

- After the presentation, participants will be able to:
  - Describe risk factors for vitamin D deficiency and major sources of the vitamin
  - Understand role of vitamin D on maternal and fetal outcomes
  - Explain rationale for normalizing vitamin D levels during pregnancy
  - Give evidence-based recommendations for vitamin D supplementation in pregnancy

OVERVIEW

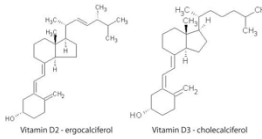
- Vitamin D sources, how it's made, metabolism
- Impact on maternal health
- Impact on fetal outcomes
- Supplementation trials

VITAMIN D BASICS

- Fat soluble vitamin, but actually a hormone
- Major function: maintain blood levels of calcium and phosphorus
- Other functions (select few):
  - bone mineralization
  - blood pressure & blood sugar regulation
  - mental health (synthesis of serotonin)
  - cardiovascular health
  - neurodevelopment
  - immune health
  - regulation of cell growth and differentiation
- **Regulates 3% of human genome**

VITAMIN D: SOURCES

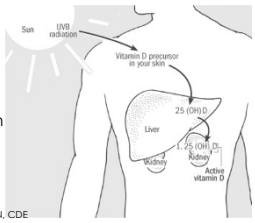
- D_3 = cholecalciferol
- D_2 = ergocalciferol



- Sunlight – D_3
- Diet – mainly D_3
- Supplements – D_3 or D_2
  - D_3 more effective at maintaining serum vitamin D levels in humans
    - Eur J Clin Nutr. 2015.

VITAMIN D + SUNLIGHT

- How it's made:
  - UVB light at correct wavelength interacts with precursor in skin, 7-dehydrocholesterol, turning it into vitamin D_3
    - Adequate sun exposure
    - Time of day
    - Time of year
    - Latitude
    - Sunscreen
    - Clothing
    - Skin color
  - Modest sun exposure, pale skin in bathing suit
    = up to 10,000-25,000 IU/day
    - Nutr. 2013.



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VITAMIN D + SUNLIGHT

- What blocks or hinders production:
  - Inadequate sun exposure
  - Time of day – max UVB rays from 10am-2pm
  - Time of year – less in winter, especially in high latitudes
  - Latitude –
    - latitudes above 33-37 = little to no production in winter
    - Boston (42), cloudless day, Nov-Feb = zero D3 synthesized
  - Sunscreen –
    - SPF 30 blocks 95% of vitamin D production
  - Clothing
  - Skin color – melanin in dark skin blocks UVB
    - requires prolonged sun exposure to produce vitamin D
    - 3-5x longer than very pale person

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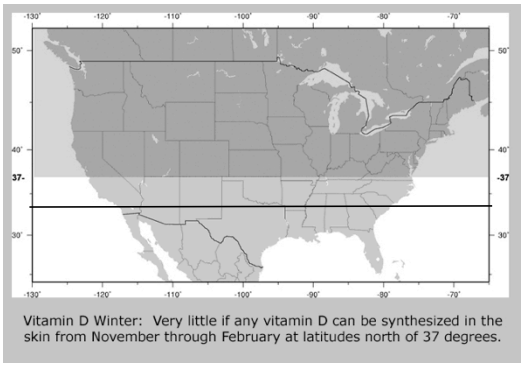

Vitamin D Winter: Very little if any vitamin D can be synthesized in the skin from November through February at latitudes north of 37 degrees.

33° latitude: Long Beach, CA – Pheonix, AZ – Birmingham, AL – Atlanta, GA

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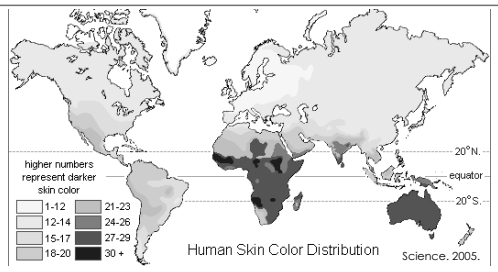
VITAMIN D AND MELANIN



Gene controlling skin pigmentation mutated~10,000 yrs ago in Europe, allowing humans living in sun-deprived environments to produce vit D

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VITAMIN D_3 PRODUCTION

- How it's made (continued):
  - Vitamin D_3 → liver → converted into 25 (OH) D
  - 25 (OH) D → kidney or other tissues → converted into 1,25 $(OH)_2D$
    - 1,25 $(OH)_2D$ = calcitriol ="active form of vitamin D"
- Note:
  - 25 (OH) D has half life of 2-3 weeks
    - Indicator of vitamin D status
  - 1,25 $(OH)_2D$ has half life of 4-16 hours
    - Not an indicator of vitamin D status
      - Breastfeed Med. 2008.

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VITAMIN D CONVERSION

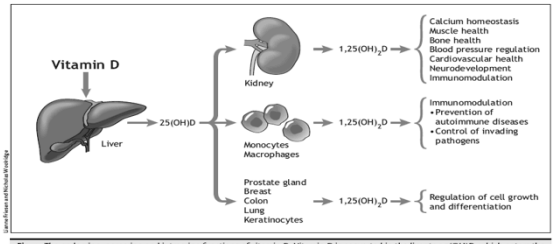

Fig. 2: The endocrine, paracrine and intracrine functions of vitamin D. Vitamin D is converted in the liver to 25(OH)D, which enters the systemic circulation and is converted to 1,25(OH)2D in a variety of end-organ tissues. As shown, 1,25(OH)2D is involved in the regulation of numerous systems.

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VITAMIN D CONVERSION, CONT'D

- The placenta can also convert vitamin D to its active form, 1,25 $(OH)_2D$. In early pregnancy, synthesis of **1,25 $(OH)_2D$ increases dramatically.**
- By 12 weeks,1,25 $(OH)_2D$ serum levels are >2x non-pregnant levels
  - They continue to rise in pregnancy, reaching **> 700 pmol/L**
    - **Non-pregnant reference range: 48–120 pmol/L**
  - These levels "would be toxic due to hypercalcemia to the non-pregnant individual, but are essential during pregnancy"
    - Bone Research. 2017

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ACTIVATED VITAMIN D

- Over 30 tissues express the vitamin D receptor, and are able to respond to 1,25 $(OH)_2D$
- Adequate 25 (OH)D directly affects 1,25 $(OH)_2D$ levels in pregnancy
- Role of activated vitamin D in pregnancy:
  - aids implantation
  - supports fetal growth through delivery of calcium
  - regulates placental function & placental hormone levels
  - limits production of proinflammatory cytokines
  - involved in maturation of fetal lungs
  - maintains endothelium integrity/membrane stability
    - Nutrients, 2015; Bone Research, 2017; Metabolism, 2017.

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VITAMIN D HOMEOSTASIS

- Pregnancy results in 3 major adaptations in vitamin D homeostasis:
  - Increase in maternal 1,25 $(OH)_2D$
  - Maintain maternal 25(OH)D availability for optimal neonatal 25(OH)D status
  - Increase of maternal VDBP concentrations
- These changes are seen in systemic + placental circulation
  - It's believed that the placenta is the major site of vitamin D metabolism in pregnancy
    - Metabolism, 2017

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VITAMIN D + DIET

- Dietary sources:
  - Fatty fish – salmon, sardines, fish eggs, fish liver
  - Organ meats, especially liver
  - Egg yolks
    - 3x higher levels if chickens are outdoors in sunlight
  - Dairy products – whole milk from pastured cows OR fortified
    - Commercial milk is fortified to 100 IU per 8oz
    - Yogurt and cheese are not always fortified
  - Animal fats of pastured animals
    - Butter, lard, tallow *if* animal received adequate sunlight
  - Fortified foods
    - Typically 100 IU or less per serving
  - Mushrooms
    - Small amounts of vitamin D_2 if grown under UVB light
      - Br J Nutr. 2012; Plos One. 2013; Adv. Nutr. 2013.

VITAMIN D + DIET

- Diet is generally considered a poor source of vitamin D
- UVB rays from sun are the primary source
  - Sun exposure accounts for ~90% of vitamin D in the body in individuals who do not take supplements
    - Am J Clin Nutr. 2004.
- If sun exposure is inadequate, supplementation is required to meet the body's needs

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CO-FACTORS

- Nutrients that work synergistically with vitamin D:
  - Magnesium
  - Vitamin A
  - Vitamin K2
  - Calcium
  - Zinc
  - Boron

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VITAMIN D: NORMAL LEVELS

- Deficiency < 20 ng/ml (50 nmol/L)*
- Insufficiency < 30 ng/ml
- Normal >30 or 32 ng/ml

- Optimal levels debated ~ 30-80 ng/ml
  - Lifeguards = 70 ng/ml
  - Native tribal, nomadic Africans (including preg) = 46 ng/ml
    - Br J Nutr. 2012.

- Rickets/osteomalacia < 10 ng/ml

- ***25 (OH) D levels**
- ***Unit conversion 1 ng/ml = 2.5 nmol/L**

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VITAMIN D: REQUIREMENTS

- IOM – pregnant or breastfeeding
  - EAR: 400 IU
  - RDA: 600 IU/day
  - Upper Limit (UL): 4,000 IU/day

- Endocrine Society – pregnant or breastfeeding
  - Recommend 1,500-2,000 IU/day
  - UL: 10,000 IU/day

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VITAMIN D: SCREENING

- American College of Obstetricians and Gynecologists (ACOG):
  - Vitamin D screening and supplementation during pregnancy is *not* required unless women:
    - Live in cold climates
    - Reside in Northern latitudes
    - Wear sunscreen and protective clothing
    - Are ethnic minorities
    - Are vegetarian

  - **What % of your patients meet at least one of the criteria above?**

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VITAMIN D DEFICIENCY

- **Estimated that 20-85% of pregnant women are deficient in vitamin D worldwide**

- Rates of deficiency vary by country of origin, skin color, latitude, etc.

- Women of color at highest risk. Black women have 6-fold higher risk of deficiency compared to white women
  - J Nutr. 2007.

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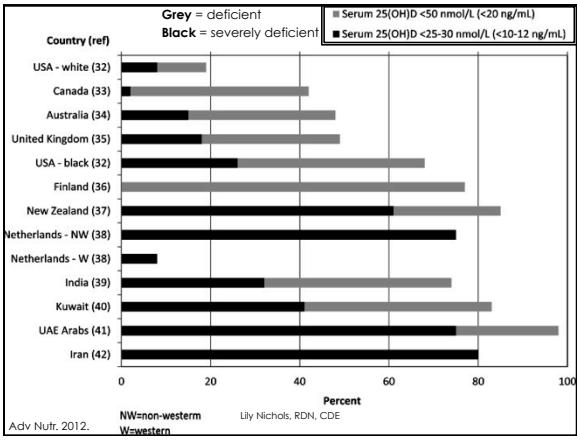

Adv Nutr. 2012.

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VITAMIN D DEFICIENCY

- **High prevalence of vitamin D deficiency in areas far from the equator**

- Longitudinal study of 99 pregnant women in Northern Ireland (latitude 54-55°N)

- 25(OH)D measured at 12, 20, and 35 wks gestation
  - **96% were vitamin D deficient (<20ng/ml)**
    - Br J Nutr. 2009.

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VITAMIN D DEFICIENCY

- **Deficiency is common even at latitudes where year-round UVB exposure is expected to be adequate**
- Study of 494 pregnant women in South Carolina (latitude 32°N)
- 25 (OH) D measured at 14 weeks gestation
  - Deficiency ≤ 20ng/ml
    - 154 African-American – **97% deficient**
    - 194 Hispanic – **81% deficient**
    - 146 Caucasian – **67% deficient**
      - Amer J Perinatol. 2011.

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VITAMIN D DEFICIENCY

- **Dark-skinned women in Northern latitudes at highest risk. Current RDA may be insufficient.**
- Study of 40 healthy mother-infant pairs. Mostly black. Living in Michigan (latitude >42°N)
- Moms ingested 600 IU Vitamin D_3 daily (PNV + 2 glasses milk)
- At birth:
  - **76%** of mothers were deficient (<20 ng/ml)
  - **81%** newborns were deficient (<20 ng/ml)
    - Child Pediatr. 2007.

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VITAMIN D DEFICIENCY

- Cross-sectional study of pregnant women in Norway
- 25 (OH) D measured:
  - 1st trimester
  - 2 days postpartum
- Mean vitamin D intake (572 IU) met Nordic recommendations, yet:
  - **71%** of women were deficient (<20 ng/ml)
    - J Clin Endocrinol Metab. 2010.

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CONSEQUENCES OF VITAMIN D DEFICIENCY

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MATERNAL EFFECTS OF DEFICIENCY

- Meta-analysis of 24 studies found mothers with 25 (OH) D < 20ng/ml had higher risk of:
  - Gestational diabetes [OR 1.38]
  - Preeclampsia [OR 2.09]
  - Preterm birth [OR 1.58]
  - Small for gestational age [OR 1.52]
    - *J Matern Fetal Neonatal* Med. 2013.
- Meta-analysis of 31 studies found similar results:
  - Gestational diabetes [OR 1.87]
  - Preeclampsia [1.79]
  - Small for gestational age [1.85]
    - BMJ. 2013.

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MATERNAL EFFECTS OF DEFICIENCY

- Low maternal vitamin D is also associated with:
  - Bacterial vaginosis
    - J Am Obstet Gynecol. 2017.
  - Maternal periodontal disease
    - Arch Womens Ment Health. 2015.
  - Postpartum depression
    - J Am Psychiatr Nurses Assoc. 2010.
  - C-Section
    - PloS one. 2015.
  - Prolonged or obstructed labor
    - J Am Perinatol. 2015.
  - Recurrent pregnancy loss
    - Hum Reprod. 2014.

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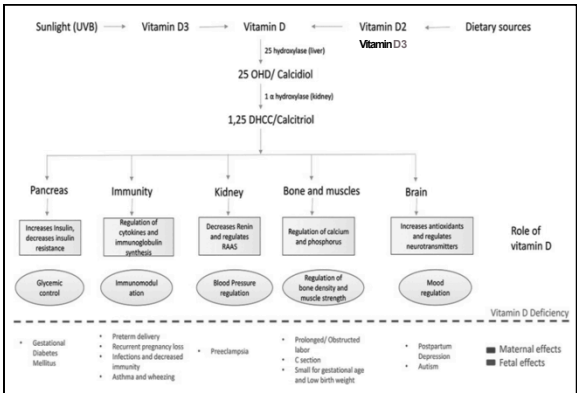


VITAMIN D AND PREECLAMPSIA

- Nested case-control study from Canada
  - 169 cases of preeclampsia; 1975 controls
- 25(OH)D measured at <20 weeks
- Women who developed preeclampsia had significantly lower vitamin D levels
- Women with 25(OH)D <12 ng/ml had a 2.2x greater risk of preeclampsia compared to women with >20 ng/ml
  - J Am Obstet Gynecol. 2015.

PREECLAMPSIA: VITAMIN D MECHANISM OF ACTION

- Compared to normal pregnancy, in preeclampsia:
  - Activation of vitamin D to $1,25(OH)_2D$ is decreased
  - Catabolism of $1,25(OH)_2D$ increased
  - Placental accumulation of vitamin D is impaired
  - Placental uptake of vitamin D binding protein is dysregulated
    - Placenta, 2017.

VITAMIN D AND POSTPARTUM DEPRESSION

- Turkish study on postpartum depression (PPD)
  - Follow-up to Robinson et al study, in which women in the lowest quartile (<18.8 ng/ml) for Vitamin D at 18 weeks gestation were more likely to have postnatal mood disturbances
- Lower maternal vitamin D levels in 2nd trimester of pregnancy were associated with higher levels of PPD symptoms at 1 week, 6 weeks, and 6 months postpartum
  - Arch Womens Ment Health. 2015.

PRECONCEPTION VITAMIN D & PREGNANCY LOSS

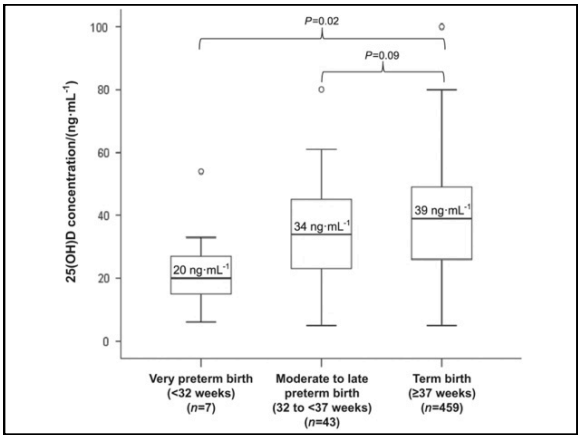
- Secondary analysis of data from EAGeR trial (large RCT)
  - 1191 women aged 18–40 years with 1 or 2 previous pregnancy losses in the USA
  - Vitamin D measured preconception & 8 weeks gestation
- Sufficient preconception 25(OH)D (≥30 ng/ml) was associated with increased likelihood of pregnancy and live birth.
- Sufficient 25(OH)D at preconception, *but not in early pregnancy*, were associated with reduced risk of pregnancy loss.
  - Lancet Diabetes Endocrinol. 2018.

VITAMIN D & PRETERM BIRTH

- Observational study of new vitamin D & pregnancy policies at Medical University of South Carolina (MUSC)
  - 1,064 pregnant women, ethnically diverse
- Nurse + prenatal pamphlet explained benefits of vitamin D supplements at first prenatal visit
- **Free vitamin D supplements (5,000 IU/day) were provided**
- Vitamin D screening at first prenatal visit + follow up testing each trimester
  - **Treatment goal was ≥40 ng/ml**
  - PLoS One. 2017.

VITAMIN D & PRETERM BIRTH, CONT'D

- Women with >40 ng/ml vs. 20 ng/ml had significantly lower risk of preterm birth regardless of type of preterm birth:
  - **Spontaneous: 58%**
  - **Medically indicated: 61%**
- Among women with initial 25(OH)D <40 ng/mL, preterm rates were **60% lower** for those with ≥40 vs. <40 ng/mL on a follow-up test
  - **For non-Caucasian women, 78% reduction**
  - PLoS One. 2017.



VITAMIN D AND GDM

- $1,25(OH)_2D$ regulates insulin secretion by pancreatic β cells
- Low 25(OH)D is a risk factor for glucose intolerance and insulin resistance
- Early pregnancy vitamin D deficiency significantly increases risk for GDM
  - Paediatr Perinat Epidemiol. 2015.
- GDMs have higher prevalence of vitamin D deficiency (<20 ng/ml)
  - Curr Diab Rep. 2014.

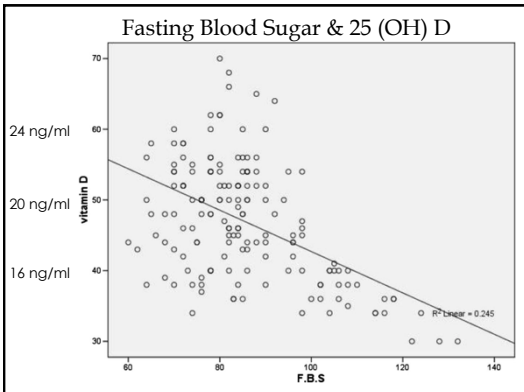
VITAMIN D AND GDM

- Risk of GDM increases **40%** for each standard deviation decrease in 25 (OH) D (7.5 ng/ml)
  - independent of adiposity, age, or season of blood sampling
- First trimester 25 (OH) D deficiency increases risk of GDM (using IADPSG 75g OGTT criteria)
  - European Association for the Study of Diabetes (EASD) 48th Annual Meeting. 2012.

VITAMIN D AND GDM

- Cross-sectional study of 160 pregnant women in their third trimester (half with GDM, half without)
  - Study performed in Egypt; majority of participants wear a veil
- Average vitamin D levels similar in both GDM and non-GDM women (20 ng/ml vs. 19 ng/ml)
  - **i.e. BOTH groups are deficient**
- Among women with GDM: **higher fasting blood sugar, fasting insulin levels, and HbA1c** correlated with low vitamin D levels (statistically significant)
  - BMC Pregnancy Childbirth. 2014

Fasting Blood Sugar & 25 (OH) D



BMC Pregnancy Childbirth. 2014

VITAMIN D AND GDM

- Observational study of 147 women with GDM in Australia
- 41% deficient in vitamin D
  - Deficiency more common in Indian & Middle Eastern women
- 25 (OH) D levels were inversely associated with:
  - fasting and 2 hr BG (during 75g OGTT)
  - HbA1c
- 25 (OH) D found to be independent predictor of HbA1c
  - Association remained significant even after excluding abnormal HbA1c values (defined as > 6%)
    - Med J Aust. 2011.

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VITAMIN D AND GDM

- Compared to GDMs with adequate 25(OH)D levels (>20 ng/ml), GDMs with low vitamin D status had mean differences of:
  - Fasting blood sugar **7.2 mg/dl higher**
  - 1 hour glucose **43.2 mg/dl higher**
  - HbA1c **0.4% higher**
    - Med J Aust. 2011.

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VITAMIN D AND GDM

- Cohort study of 1,873 women >24 wks
- Severe vitamin D deficiency (<10 ng/ml) was significantly more common in women with GDM (16.5% vs 11%)
- Deficient women had less exposure to sunlight, lower use of vitamin D supplements, and less physical activity
  - Int J Women's Health. 2013.

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VITAMIN D AND T1DM

- Observational study on T1DM pregnancy and vitamin D
  - 65 pregnant T1DM
  - 52 pregnant controls
- Vitamin D deficiency common in both groups ~85%
- T1DMs with lower vitamin D levels had significantly higher HbA1c
  - PLoS One. 2013.

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FETAL EFFECTS OF VITAMIN D DEFICIENCY

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VITAMIN D IMPACT ON FETUS

- Stores of vitamin D in the infant are dependent on maternal vitamin D status
- **25 (OH) D** passes from placenta to fetus
- Maternal $1,25(OH)_2D$ does <u>not</u> cross the placenta, however, the placenta can synthesize $1,25(OH)_2D$ directly from 25 (OH)D
  - Ann Nutr Metab. 2018.

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TRANSFER TO FETUS

Transfer of vitamin D metabolites from mother to fetus and relative concentrations:

Mother	Placenta	Fetus
↑ Vitamin D	→	Vitamin D ↓
↑25 (OH) D	→	25 (OH) D ↓
↑ $1,25(OH)_2D$		$1,25(OH)_2D$ ↓

Generally, cord blood 25(OH)D level is between 50% and 80% of the maternal serum level.

Am J Clin Nutr 2008;88:529S-533S

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VITAMIN D TRANSFER + OBESITY

- Vitamin D transfer may be related to maternal weight
- Cross-sectional study of 61 maternal-neonatal pairs (obese vs normal weight moms)
  - Measured 25(OH)D at 36-38 weeks and cord blood at delivery
- Obese women transfer *significantly less* 25(OH)D to offspring than normal weight women
  - Despite similar and sufficient maternal serum levels in both groups (46-49 ng/ml)
- Cord blood 25(OH)D had direct inverse association with neonatal percent body fat
  - J Clin Endocrin Met. 2013.

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VITAMIN D TRANSFER + OBESITY (ANOTHER STUDY)

- Analysis of subset of data from Hyperglycemia and Adverse Pregnancy Outcomes (HAPO)
  - Caucasian women, residing at latitudes 41–43°, 39–41 weeks
  - Healthy pregnant women had a 75-g fasting oral glucose tolerance test (OGTT) at ~28 weeks
- Every 1-point increase in maternal BMI (kg/m^2) was associated with:
  - Vitamin D levels 0.26 ng/ml lower in cord blood ($p<0.004$)
  - Vitamin D levels 0.40 ng/ml lower in maternal blood ($p<0.001$)
- Birth weight and neonatal adiposity NOT associated with vitamin D levels
  - PloS one. 2016.

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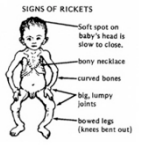
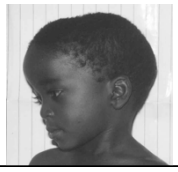
MATERNAL VITAMIN D AND FETAL BONE DEVELOPMENT

- Vitamin D is well known to influence calcium uptake and bone metabolism
- In infants with rickets, 91% of moms had vitamin D levels <10 ng/ml (severe deficiency)
  - Clin Nutr . 2015.



FETAL BONE DEVELOPMENT

- Maternal vitamin D deficiency is associated with craniotabes in infants, a softening of skull bones
  - Clin Nutr. 2015.
- Craniotabes may be one of earliest sign of vitamin D deficiency and nutritional rickets
  - J Clin Endocrinol Metab. 2008.



FETAL BONE DEVELOPMENT

- Although nutritional rickets is rare, incidence has increased significantly from the year 2000
  - Mayo Clin Proc. 2013.
- In a review study of US rickets cases from 1986-2003,
  - 83% of children with rickets were African American or black
  - 96% were breast-fed. Among children who were breast-fed, only 5% received vitamin D supplements
  - Only incidence of rickets in white children were those living in northern latitudes
    - Am J Clin Nutr. 2004

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FETAL BONE DEVELOPMENT

- Prospective longitudinal study of pregnant adolescents <18yrs old followed from 26 wks to term
  - Measured serum vit D and fetal bone development (via sonograms)
- Moms with adequate vitamin D (>20 ng/ml) had infants with significantly longer femur and humerus bones
- Calcium intake was only associated with appropriate BMD in femur when maternal vitamin D was >20 ng/ml
  - Am J Clin Nutr. 2012.

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BONE HEALTH LATER IN LIFE

- Children of mothers with low vitamin D status during late pregnancy have reduced whole body bone mineral content, bone area, and areal bone mineral density at age 9
  - Lancet. 2006.
- Maternal vitamin D deficiency at 18 weeks' gestation is associated with lower peak bone mass among children at 20 years of age
  - J Bone Miner Res. 2014.
- **Suggests maternal vitamin D influences lifetime bone health in offspring**

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OTHER FETAL EFFECTS

- Maternal vitamin D deficiency may also be associated with long term health of the child, increasing risk of:
  - Allergies, asthma, and eczema
    - JAMA, 2016; Pediatr Allergy Immunol Pulmonol. 2015.
  - Language impairment
    - J Pediatr. 2015.
  - Schizophrenia
    - FASEB J. 2015.
  - T1DM
    - PloS one. 2017.
  - Multiple Sclerosis
    - JAMA Neurol. 2016.
  - Autism
    - Eur Child Adolesc Psychiatry. 2016.

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NEONATAL VITAMIN D STATUS

- Neonatal vitamin D status can be measured via cord blood at delivery
- Currently, sufficient neonatal 25(OH)D is defined as > 20 ng/ml
- Cord blood 25(OH)D >30 ng/mL has been associated with:
  - improved newborn innate immune response
  - reduced risk of respiratory syncytial virus bronchiolitis
  - reduced risk of eczema in early childhood
    - Eur J Clin End & Met. 2011; Pediatrics. 2011; Pediatrics. 2012.

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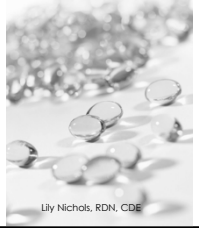
SAFETY OF SUPPLEMENTS?

- If maternal vitamin D deficiency has negative consequences on both mother and baby, how safe are supplements?



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SUPPLEMENTATION

- Cochrane review in 2012 looked at 6 trials with a total of 1023 women
- Objective: examine whether supplements with vitamin D given to women during pregnancy can safely improve maternal and neonatal outcomes
- Evaluated effect of:
  - Vitamin D alone versus no treatment/placebo (no vitamins or minerals)
  - Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)
  - Vitamin D + calcium versus calcium (but no vitamin D)
  - Vitamin D + calcium + other vitamins and minerals versus calcium + other vitamins and minerals (but no vitamin D)

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COCHRANE CONCLUSIONS

- Vitamin D supplementation during pregnancy increases maternal 25(OH)D
- Inadequate number of high quality trials and outcomes reported to draw conclusions on vitamin D supplementation for maternal or fetal outcomes
- Suggested more RCTs to evaluate the role of vitamin D supplementation in pregnancy

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COCHRANE REVIEW: CRITICS

- Omitted an RCT using 400 IU of vitamin D as a control group
- Grouped all levels of vitamin D supplementation
  - Main outcome measured was effect of vitamin D supplement vs. no vitamin D supplement, not what level of supplementation was most effective
  - Well established that low levels of supplementation may not correct vitamin D deficiency
- No separate analysis to assess role of ethnicity or latitude

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COCHRANE UPDATES

- 2016 Update now includes 15 trials (2833 women)
  - 9 compare vitamin D alone vs. no treatment
  - 6 compare vitamin D + calcium vs. no treatment
- Conclusions: vitamin D supplementation significantly raises serum 25(OH)D levels, particularly if supplementation is daily versus weekly, monthly or once
- Vitamin D supplementation, with or without calcium, may reduce the risk of preeclampsia
- Observational studies have found an association between vitamin D and lower rates of GDM and C-section

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CRITICS OF COCHRANE

- **Trials comparing differing doses of vitamin D supplements were not included**
- This includes 2 studies by Hollis et al., which found significant beneficial effects of high doses of vitamin D supplementation (4000 IU/d) compared to lower dose (400 or 2000 IU/d) during pregnancy on pre-eclampsia and caesarean section.
- There are currently ~15 ongoing trials that could contribute additional data
  - J Steroid Biochem Mol Biol. 2016.

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RCTs on VITAMIN D SUPPLEMENTATION

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1ST SUPPLEMENTATION RCT

- Double blind, RCT on safety and effectiveness of vitamin D supplementation in pregnancy
  - J Bone Miner Res. 2011.
- Goal = normal 25(OH)D in mother and infant
- 350 healthy pregnant women given daily vitamin D_3 supplements of 400 IU (control), 2,000 IU, or 4,000 IU starting at 12-16 wks gestation
  - Caucasian 32%
  - African American 28%
  - Hispanic 40%

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1ST SUPPLEMENTATION RCT

- Vitamin D measured each trimester
- Changes in maternal vitamin D levels:

	Mean Maternal 25(OH)D Levels (ng/ml)			
Treatment	Baseline	2nd Trimester	3rd Trimester	% sufficient at delivery
400 IU	24.5	30.4	32.5	**50.0%**
2,000 IU	23.0	33.7	41.0	**70.8%**
4,000 IU	23.9	39.4	45.8	**82.0%**
p-value	0.5	**<0.0001**	**<0.0001**	**<0.0001**

- Vitamin D sufficiency defined as 25(OH)D ≥ 32 ng/ml

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SUPPLEMENTATION RCT RESULTS

- Outcome on infant vitamin D levels:

Treatment	Mean cord blood vitamin D levels at birth (ng/ml)	% of infants reaching **sufficient** vitamin D levels
400 IU	18.2	**39.7%**
2,000 IU	22.8	**58.2%**
4,000 IU	26.5	**78.6%**
p-value	**<0.0001**	**<0.0001**

- Infant vitamin D levels >20 ng/ml considered sufficient
- Maternal intake of 400 IU/day (EAR) resulted in ~60% of infants deficient at birth

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SUPPLEMENTATION RCT RESULTS

- Vitamin D levels by race and trimester

Treatment	**400 IU**			**2,000 IU**			**4,000 IU**		
	Mean Maternal 25(OH)D Levels (ng/ml)								
Race	B	2nd	3rd	B	2nd	3rd	B	2nd	3rd
Black	14.9	19.5	**19.8**	16.4	28.9	**36.5**	16.3	32.4	**39.1**
Hispanic	23.6	31.0	**31.8**	23.7	34.1	**40.1**	25.4	40.6	**48.4**
White	32.5	38.1	**42.8**	28.8	38.0	**45.0**	28.5	43.9	**48.2**
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.02	<0.0001	<0.0001	<0.008

- Dark skinned women may require more vitamin D

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SUPPLEMENTATION RCT RESULTS

- Levels of active vitamin D 1,25(OH)$_2$D were also measured
- 1,25(OH)$_2$D levels normalized when 25 (OH)D levels reached >40 ng/ml
  - Suggests that achieving 40 ng/ml may be optimal during pregnancy

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SUPPLEMENTATION RCT RESULTS

- Vitamin D supplementation resulted in significantly lower rates of:
  - Primary C-section (p = 0.046)
  - Hypertensive disorders of pregnancy (p = 0.05)
  - Comorbidities of pregnancy (p = 0.03)
- Rates of GDM also decreased with vitamin D supplements (results did not reach statistical significance)

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SUPPLEMENTATION RCT RESULTS

- No significant differences in serum calcium, creatinine, phosphorus, urinary calcium/creatinine ratios between supplementation groups
- No single adverse events attributed to vitamin D supplementation or circulating vitamin D levels
- No hypervitaminosis D was observed (defined as 25(OH)D >150ng/ml)
  - "The only known avenue of vitamin D toxicity is manifested through hypercalcemia and hypercalciuria, neither of which was observed in our RCT." - Hollis

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SUPPLEMENTATION RCT LIMITATIONS

- Study was completed at 32 degrees latitude
  - Vitamin D obtained from sun exposure may confound results
  - Women in northern latitudes may require more vitamin D
- Subjects were not severely deficient at baseline
  - Mean 25 (OH) D for all subjects = 23.8 ng/ml
  - Higher doses of vitamin D may be needed in severely deficient women
- Focus was normalizing vitamin D levels, not comorbidities. Need further studies.

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2ND SUPPLEMENTATION RCT

- Similar study design to previous RCT by Hollis
  - 257 pregnant women 12–16 weeks; South Carolina; ethnically diverse
  - 2000 IU vs. 4000 IU/day

	Maternal 25(OH)D		Infant 25(OH)D
Treatment	Baseline	3rd Trimester	Cord Blood
2,000 IU	22.7	36.2	22.1
4,000 IU	22.7	37.9	27.0

- After controlling for race and study site, preterm birth and labor were inversely associated with pre-delivery 25(OH)D.
  - AJOG. 2013.

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3RD SUPPLEMENTATION RCT

- Another similar RCT confirmed safety of prenatal vitamin D supplementation above RDA
  - Arab women in UAE
- 192 women supplemented with 400 IU (control), 2,000 IU, or 4,000 IU
- 4,000 IU group had highest % of vitamin D sufficiency in both mother and their infants
- No adverse events
  - J Clin Endocrinol Metab. 2013.

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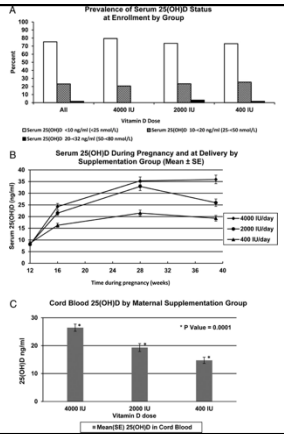

- 75% of participants SEVERELY deficient; 99% insufficient
- **Only ONE participant had 25(OH)D levels above 32 ng/ml**
- 2,000 IU is not sufficient to normalize 25(OH)D levels in severely deficient women
- Women receiving 4,000 IU vs. 400 IU are 7x more likely to reach normal vitamin D levels at delivery
- Only 4,000 IU group had infants with normal 25(OH)D levels

Categories of Maternal and Infant Vitamin D Status at Delivery by Treatment Group

	4000 IU (n = 43)	2000 IU (n = 41)	400 IU (n = 42)	*P* Value
Mothers achieving 25(OH)D ≥ 32 ng/mL (≥80 nmol/L), n, %	28 (65.1)	10 (24.4)	4 (9.5)	.0001
Mothers achieving 25(OH)D ≥ 20 ng/mL (≥50 nmol/L), n, %	39 (90.7)	31 (75.6)	20 (47.6)	.0001
Infants achieving 25(OH)D ≥ 20 ng/mL (≥50 nmol/L), n, %	34 (79.1)	18 (43.9)	9 (21.4)	.0001

Categories of Maternal and Infant Vitamin D Status in This Study and US Study[25]

	4000 IU		2000 IU		400 IU	
	UAE	US	UAE	US	UAE	US
Mean baseline 25(OH)D, ng/mL	7.8	23.3	8.2	23.3	8.6	24.6
Mean 25(OH)D at delivery, ng/mL	35.9	44.0	25.9	39.3	19.3	31.6
Mothers achieving 25(OH)D ≥ 32 ng/mL, %	65	82	24	71	10	50
Infants achieving 25(OH)D ≥ 20 ng/mL, %	75	79	47	58	22	40

4TH SUPPLEMENTATION RCT

- Tested high-dose vitamin D supplementation on obstetric complications + birth outcomes
  - Study performed in India
- 180 women (control group vs. vitamin D supplemented group)
- **Vitamin D supplemented group split into 3 arms** with dosage of vitamin D supplements based on serum 25 (OH)D levels.

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4TH SUPPLEMENTATION RCT

- If vitamin D was **sufficient**, ONE dose of 60,000 IU D3
  - at 20 weeks
- If vitamin D was **insufficient**, TWO doses of 120,000 IU D3
  - at 20 weeks and 24 weeks
- If vitamin D was **deficient**, FOUR doses of 120,000 IU D3
  - at 20, 24, 28 and 32 weeks

- "Sufficient" (>20 ng/ml) received total of 60,000 IU
  - Average of 3,000 IU/week
- "Insufficient" (10-20 ng/ml) received total of 240,000 IU
  - Average of 12,000 IU/week
- "Deficient" (<10 ng/ml) received total of 480,000 IU
  - Average of 24,000 IU/week

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4TH SUPPLEMENTATION RCT

Vitamin D Levels → **Treatment**	**Maternal Baseline 25(OH)D**	**Maternal 25(OH)D at Delivery** % who achieved >20 ng/ml	**Infant 25(OH)D** % who achieved >20 ng/ml
Unsupplemented	9.6 ng/ml	14%	14%
Supplemented 60,000 IU 240,000 IU 480,000 IU	 >20 ng/ml 10-20 ng/ml <10 ng/ml	 89% 85% 53%	 46% (collective total)

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4TH SUPPLEMENTATION RCT

- Sufficient vitamin D levels (>20 ng/ml) were seen in 93.3% patients who had **>4 h of sun exposure every day** as compared to 1.9% in those with <1 h of daily sun exposure (P = 000).
- "A strong association was found with religion, more Muslims were found to have vitamin D deficiency as compared to Hindus (75% vs 45%)."
- Women in the supplemented group had significantly lower rates of gestational diabetes, preeclampsia, and preterm birth
  - Clin Endocrinol. 2015.

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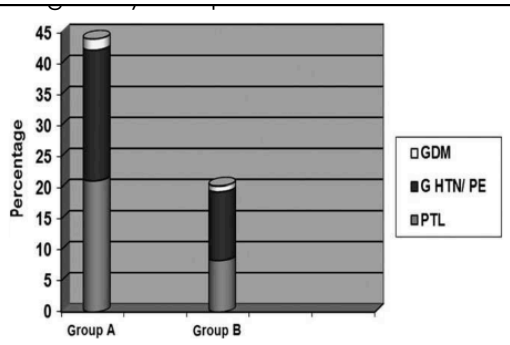

Fig. 2 Prevalence of pregnancy related complications in non-intervention (Group A) and Intervention group (Group B).

4TH SUPPLEMENTATION RCT

- Supplementing with a large bolus of vitamin D is safe in pregnancy (if preferred over daily dosing)
- "Pregnant women with risk factors for vitamin D deficiency (inadequate sun exposure, high BMI and poor nutritional intake) can be safely given a total of 480 000 IU divided in four doses of 120 000 IU each at 20, 24, 28 and 32 weeks of gestation."
- My thoughts:
  - Would be best to calculate out daily dosage to ensure adequate intake
  - Good study design to supplement based on 25 (OH)D status

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5TH SUPPLEMENTATION RCT

- 193 Pakistani women
- Vitamin D (4,000 IU, started at 20 weeks) vs. routine care (no vitamin D, routine calcium + iron supplements)
- Measured maternal 25 (OH)D at baseline and delivery + Neonatal 25(OH)D via cord blood OR 48 hours after birth

Vitamin D	**Mother (ng/ml)**		**Infant (ng/ml)**
	Baseline	Delivery	Cord or 48hr
No vitamin D	6.3	6.9	6.3
4,000 IU	8.8	18.3	19.2

- J Clin End & Met. 2014.

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5TH SUPPLEMENTATION RCT

- Both 1 and 5 minute Apgar scores were significantly higher among infants in the vitamin D supplemented group
- In supplemented group, doses of 4,000 IU/day were inadequate to correct severe maternal vitamin D deficiency
- Suggests higher doses may be needed for severely deficient women

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6TH SUPPLEMENTATION RCT

- Goal: assess impact of prenatal vitamin D supplementation on infant immune system
  - subset of VDAART study on asthma + vitamin D
- 51 women; supplementation began in 2nd trimester
  - Control: placebo pill + 400 IU from PNV
  - Treatment: 4,000 IU + 400 IU from PNV (4,400 IU total)
- Measured vitamin D levels (mother and cord blood) & markers of child immune system

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6TH SUPPLEMENTATION RCT

	Maternal Baseline	Maternal 3rd trimester	Infant Cord blood
400 IU	23.5 ng/ml	24.6 ng/ml	16.2 ng/ml
4400 IU	**19.2 ng/ml**	**35.4 ng/ml**	**25.4 ng/ml**

- Cord blood analysis revealed "enhanced activation of innate immune system"
- "Vitamin D exposure during fetal development influences the immune system of the neonate, which can contribute to protection from asthma-related, including infectious, outcomes in early life."

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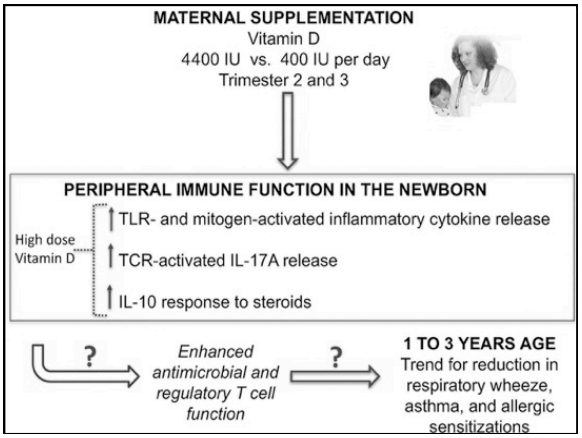

HOW TO ENSURE MOTHERS GET ENOUGH VITAMIN D?

- Only way to assess vitamin D adequacy is to check serum 25 (OH) D
  - Identify and test at-risk patients
- Encourage regular sun exposure or consider supplementation
- Due to the variables that affect skin synthesis of vitamin D and skin cancer concerns, it is difficult to recommend a specific amount of sunlight exposure for all populations

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ACOG GUIDELINES FOR SUPPLEMENTATION

- At risk patients to screen:
  - Live in cold climates
  - Reside in Northern latitudes
  - Wear sunscreen and protective clothing
  - Are ethnic minorities
  - Are vegetarian
- "When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 international units per day of vitamin D is safe."
  - ACOG Committee Opinion. 2011 (Reaffirmed 2017).

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VITAMIN D NEEDS

- Some research suggests estimated requirements for vitamin D were set far too low
  - Read: "A Statistical Error in the Estimation of the Recommended Dietary Allowance for Vitamin D" and "The Big Vitamin D Mistake"
- They argue the RDA for vitamin D should have been set at 7,000-8,000 IU per day to maintain adequate blood levels of 25(OH)D for majority of adults
- As always, further research is needed
  - *J Prev Med & Pub Health*. 2017; *Nutrients*. 2014.

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RCT FINDINGS

- Suggest that 4,000 IU/day is safe and effective at raising maternal and neonatal vitamin D levels and may prevent certain complications
- Some populations may require doses greater than 4,000 IU/day to achieve sufficient vitamin D levels
- Ideal to adjust supplement dosage on 25(OH)D status

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CLINICAL TAKEAWAYS

- Maintaining serum levels of 40 ng/ml appears optimal
  - Provides adequate substrate for optimizing 1,25 (OH)D levels
  - Close to hunter-gatherer 25(OH)D levels (physiological norm!?)
- If possible, test vitamin D status prior to or early in pregnancy, as it plays a role in implantation & needs increase in pregnancy
- Maintain vitamin D intake throughout pregnancy & postpartum

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SUMMARY

- High prevalence of vitamin D deficiency in pregnant women
- Maternal vitamin D deficiency may:
  - increase the risk of pregnancy complications
  - lead to deficiency in her baby, which carry lifetime health risks
- Supplementation above the RDA is safe and often necessary to normalize maternal & fetal vitamin D levels

MORE WEBINARS COMING!

WOMEN'S HEALTH
NUTRITION ACADEMY

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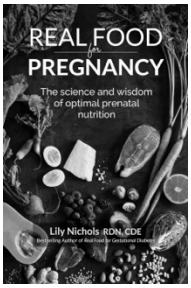
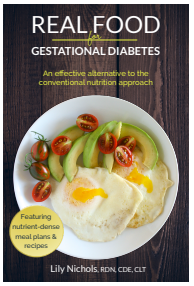
MORE ON PRENATAL NUTRITION





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