DEFICIENT LEVELS OF VITAMIN D DURING PREGNANCY MAY ADVERSELY AFFECT BIRTH OUTCOMES AND NEWBORN HEALTH

BY

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Abstract

Objective: Vitamin D is an essential nutrient during pregnancy due to rapid growth of bone development in the fetus. It is hypothesized that low levels of maternal serum 25(OH)D lead to a disruption of neonatal calcium absorption and affect intrauterine growth, premature labor, maternal blood pressure, newborn birth weight; and possibly potentiate an increased risk of cesarean delivery, and an increased risk of newborn complications. Current levels of vitamin D are inadequate in most areas of the United States with certain populations experiencing a further risk of deficit. *Data Sources:* CINAHL, PubMED, Medline, Proquest, Google Scholar, and UpToDate were used for reviewing the literature. *Study Selection:* In this review, past and current studies were reviewed to support or refute the explored hypothesis. *Data Extraction:* No official data extraction tools were implemented in this review. *Data Synthesis:* To date there is an inadequacy of large randomized studies to support vitamin D as a factor in adverse birth outcomes; however, there is enough evidence to support supplementation during pregnancy and in the newborn period for the prevention of osteomalacia and rickets. *Conclusions:* As more research is done involving pregnant women, recommended 25(OH)D levels and the amount of vitamin D supplementation will become clear for patients and practitioners.

Key Search Words/Terms:

Key search words were: vitamin D, birth outcomes, preeclampsia, pregnancy, rickets, cesarean section, ultraviolet radiation, UVB, sunlight and calciferol.

Introduction

Experts across the world believe current recommendations for vitamin D are insufficient to meet the needs of pregnant women (Camillo, 2008; Hollis, 2007; Scholl & Chen, 2008; Ward, Gaboury, Ladhani, & Zlotkin, 2007). In the US, the recommended daily requirement is 200 IU/day. Studies have shown ninety percent of the women who take this amount in a daily multivitamin will have deficient levels of vitamin D, with the lowest numbers during the winter months (Bodnar, et al, 2007; O'Riodan, Kiely, Higgins, & Sahman, 2008; Schroth, Lavelle, & Moffatt, 2005). Over one billion individuals across the globe have a deficiency or insufficiency of vitamin D (Holick, 2007; Malone & Kessenich, 2008).

During the second and third trimester of pregnancy, vitamin D requirements increase to meet the demands of rapid bone growth in the fetus. A deficiency of vitamin D has been shown to lead to brain damage in animal studies (Almeras, Eyles, & Benech, 2007; Feron, Burne, & Brown, 2005; Nelson & Zeratsky, 2009). Though more research is needed for supporting the role vitamin D has for both mother and infant, it appears this vitamin is important because it contributes to improving pregnancy outcomes, including decreasing the risks of pre-eclampsia, birth weight, and premature delivery. Other studies are finding high levels of vitamin D during pregnancy protects the fetus in later life from schizophrenia, brain tumors, asthma, multiple sclerosis, autism, and autoimmune diseases (Camillo, 2008; Cannell, Hollis, Zasloff, & Heaney, 2008; Malone & Kessenich, 2008; Nelson & Zeratsky, 2009; Poduje, Sjerobabski-Masnec, & Ozanic-Bulic, 2008).

History

Rickets, the precursor to the discovery of the role vitamin D plays in the human body, was first described in 1645 by Dr. Daniel Whistler and Professor Francis Glisson. In 1919, Sir Edward Mellanby discovered that the dogs he was raising indoors did better and avoided rickets when he fed them cod liver oil. The connection of sunlight and Vitamin D levels was made in 1922 when Alfred Hess, a New York pediatrician and nutrition pioneer, reported that irradiated skin fed to rats prevented them from developing rickets. It was during this time that the science of nutrition was experiencing rapid growth and vitamin D (calciferol) was first classified as a vitamin. In 1936, it become clear its mechanisms were that of a steroid rather than a vitamin (Kumaravel, Greenspan, Thomas, & Hollick, 2007). A vitamin by definition is not available in the body and must be supplemented. This description does not hold true for vitamin D which is produced in the body in the presence of adequate sunshine. After absorption through the skin, it is metabolized by the liver to form 25(OH)D and by the kidneys to form 1,25(OH)D, a steroid hormone. This hormone along with calcium and phosphorus are tightly regulated by parathyroid hormone. If one of these levels are abnormal, the others should be assessed.

Literature Review

Vitamin D has become a hot research topic over the past few years with 741 clinical trials reported by the National Institutes of Health (NIH) with every body system, nationality, gender, medical condition, and age group represented. Of these studies, seventeen are related to women during pregnancy. Past research involving pregnant women has generally focused on small groups of high risk women, often with conflicting results. The studies have also been interested in how maternal levels of vitamin D affect fetal bone development and incidence of rickets.

Only recently have studies begun to look at other physiological roles or benefits vitamin D transmits to both mom and baby.

A retrospective Swedish study published January 2010, reviewing all births in Sweden from 1900-2007 found the risk of developing multiple sclerosis higher in months that women typically have lower vitamin D levels. Though this information does support other research connecting low vitamin levels to neurological function, the researchers admit it is only one possible explanation and there may be other factors that raise the likelihood of MS.

Diagnosis and Treatment

Screening. The best method of screening is a serum 25(OH)D. It is necessary to order a $25(OH)D_3$ rather than $1,25(OH)_2D$. The differences between these two are their concentrations and half life. The later is 1000 times less concentrated in the blood, with a half life of six hours compared to two weeks with $25(OH)D_3$ (Malone & Kessenich, 2008). If ordered incorrectly the results may be high despite the patient being deficient as evidenced by low $25(OH)D_3$ level.

Ideal level of 25(OH)D. Adults, including pregnant women are recommended to keep levels between 30-60ng/ml (Bishoff-Ferrari, Giovannuci, & Willett, 2006; Geise, 2007; Malone & Kessenich, 2008). Results of 25(OH)D levels are reported as either ng/ml or nmol/l – 1 ng/ml = 2.5 nmol/l. Ideal levels have been increasing each year as more research finds higher levels to be more beneficial (Cannell, Hollis, Zasloff, & Heaney, 2008). To prevent rickets and osteomalacia, a level of 15ng/ml will be sufficient; for parathyroid suppression, an increase to 20-30ng/ml is advised; for intestinal calcium absorption, 34ng/ml. Neuromuscular performance was improved at levels of 38ng/ml; and breast cancer rates were reduced by 50% at levels of 52ng/ml (Cannell, et al.; Garland, Gorman, & Mohr, 2007). A pregnant woman needs 1000-

2000 IU of vitamin D/day, especially if she lives in a cold climate with inadequate sun exposure. The natural levels for humans working outdoors in sunny regions are 50-70ng/ml (Cannell, et al.).

Though the recommendation for breastfed infants has been established at 400 IU, others would argue 1000 IU is a more appropriate dose for children with limited sunlight (Bischoff-Ferrari, Giovannuci, & Willettt, 2006; Holick, 2007; Malone & Kessenich, 2008). Additionally some have speculated breastmilk would have adequate levels of vitamin D if the mother were to ingest 6,000 IU/day (Hollis & Wagner, 2004). The purpose of the American Academy of Pediatrics (AAP) recommendation at 400 IU is related to epidemiological and clinical studies highlighting the prevalence of hypovitaminosis in healthy children (AAP, 2008; Rajakumar, et al., 2007; Wagner & Greer, 2008). The AAP also recommends that providers measure vitamin D levels in pregnant women.

Sources of Vitamin D

Dietary. The American diet is lacking natural vitamin D. Foods that provide the best source of natural vitamin D are: fish, such as salmon, tuna, and mackerel. Smaller amounts are found in egg yolks, beef liver, and cheese. Milk fortification continues to be the best dietary source for vitamin D. Foods that are allowed to add vitamin D are: cereal flours, milk products, and calcium-fortified juices and drinks (Office of Dietary Supplements, 2005). In 2002, the vitamin D content in foods became available via the National Nutrient Database for Standard Reference. The latest information on content of vitamin D in foods was implemented by the Food Label and Package Survey in 2006-2007, placing vitamin D content on food labels (Yetley, 2008).

Solar vitamin D. No amount of sun exposure during the winter in northern latitudes will raise vitamin D levels. The UVB rays are not strong enough. Though sunscreen is important to prevent skin cancer, 15 minutes of summer sun 2-4 days/week without sunscreen will increase vitamin D to adequate levels(Malone & Kessenich, 2008). Specific wavelengths of sunlight called UVB are needed to make vitamin D in the skin 25(OH)D. The liver and kidneys then modify vitamin D into a more active form called cholecalciferol ($1,25(OH)_2D$ that is being widely studied but is most known for its function of assisting calcium absorption in bones. An example of how powerful sunlight is to vitamin D levels is explained by Hollis (2007): a fair-haired person could sunbathe for 30 minutes in the summer to produce 20,000 IU of vitamin D. This same individual would need to drink 200 glasses of milk (100 IU/8oz glass) or take 50 standard multivitamins (400 IU/day) to meet this same level of vitamin D intake (Cannell, Hollis, Zasloff, & Heaney, 2008).

The protective benefits of ultraviolet radiation and $1,25(OH)_2D$ were studied by Rolfdieter Krause, by exposing two groups of hypertensive adults to tanning beds, one with only UVA rays (similar to winter sun) and the second group to UVB (similar to summer sun). Those in the summer sun beds had on average an 180% increase in their 25(OH)D levels and an average of 6 mm Hg decrease in their systolic and diastolic blood pressure (Mead, 2008).

Supplementation. Several people are unable to obtain optimal levels of vitamin D through diet or sun exposure and are reliant on supplements to increase their 25(OH)D levels. Some factors that affecting vitamin D levels are:

- Latitude – areas farther north have longer periods of no vitamin D, for example Boston has a period of four months and northern Europe and Canada have six months

- Season
- Time of day
- Air pollution
- Clouds
- Use of sunblock – an SPF of 8 or higher blocks vitamin D absorption
- Amount of clothing covering the skin
- Older Adults
- Obese
- Color of skin

(Cannell, et al., 2008; Malone & Kessenich, 2008; Yetley, 2008).

In one Canadian study, the administration of 4,000 IU/day for six months to middle aged patients resulted in levels of 44 ng/ml and produced no adverse effects, in fact the patients reported an increased mood (Veith, Kimball, Hu, & Walfish, 2004). Some experts have recommended that 3,000 IU/day is required to assure 97% of Americans obtain levels greater 35ng/mL. Generally, the larger the patient, the larger the dose they will need of supplementation. Older adults absorb less vitamin D through the skin thus they need higher oral supplementation. Fair-skinned, thin, young, or small patients will need a lower dose than a dark-skinned, old, obese patient. A safe initial dose is 10,000 IU/day for several weeks before starting maintenance dosing (Malone & Kessenich, 2008). Supplemental types and dosages available:

- D3 – Colecalciferol, available in 400, 1000, 2000, and more recently 5,000, 10,000, and 50,000 IU capsules.

- D2 – Ergocalciferol – available in 50,000 IU (1.25 mg) capsules. Give one to two doses weekly for 8-16 weeks and then maintain levels greater 40ng/ml with 50,000 IU every 1, 2, and 4 weeks. Frequency of dosing is dependent on 25(OH)D levels, skin color, age, body weight, and sun exposure/avoidance. This supplement is two-four times less effective than colecalciferol at raising 25(OH)D levels.
- Cod liver oil – variable amounts of vitamin D and high amounts of vitamin A. Not recommended due to the effects of vitamin A minimizing the effects of vitamin D and at high levels many lead to bone toxicity.

Most vitamin D supplements are available over the counter with the exception of high doses that are prescribed for severe deficiency.

Toxicity. Also known as hypervitaminosis D occurs if a patient's vitamin D level exceeds 150 ng/ml. In order to reach this level, the patient would need to be taking more than 10,000 IU/day for many months or years (Cannell, et al., 2008). The end result is hypercalcaemia. All known cases of vitamin D toxicity with hypercalcemia have involved intake over 40,000 IU/day (Veith, 1999). Toxicity cannot occur from sun exposure. Within about 20 minutes of sun exposure, the concentration of vitamin D precursors reach their maximum balance and further vitamin D is degraded. Generally, vitamin D ingestion from the sun is limited at 20,000 IU/day.

In one unique case of toxicity a mother purchased Raquiferol ampules to promote health and strong bones in her two-year old child. Each ampule contained 600,000 IU of vitamin D. The recommended dose on the package was 2 drops/day. The mother administered one ampule, giving her child a total dose of 2,400,000 IU over a four day period. On presentation to the clinic

the patient was complaining of abdominal pain, and the mother reported he had a decreased appetite. Blood pressure was elevated at 139/98, temp 97.6, no respiratory distress, EKG showed normal cardiac rhythm, lab results were normal with the exception of an elevated calcium at 14.2 mg/dL (normal is 8.4-10.2). Vitamin D concentration was 106 ng/ml. The patient was admitted to the hospital, treated with fluids, diuretics, glucocorticoids, and a no calcium diet. On day three, the vitamin D climbed to 470 ng/ml and calcium to 15 mg/dL. During his hospital stay, the child experienced abdominal pain and persistent hypertension. With the half-life of vitamin D being 30-60 days, the patient's vitamin D level remained 376 ng/ml at discharge. Discharge instructions included avoided fluids high in vitamin D and using sunscreen (Hollis & Wagner, 2004).

Possible Adverse Birth Outcomes Related to Vitamin D Deficiency

Rickets. Thought to be more prevalent in the 19th century, it has seen resurgence. In a Canadian study involving 2325 pediatricians, 104 confirmed cases of rickets were reported over a two-year period. Though 94% were breastfed, 2.9% were formula fed. The authors suggest the formula cases were related to mothers with severely deficient levels during pregnancy and stress the importance of Vitamin D supplementation, especially in the third trimester of pregnancy (Ward, Gaboury, Ladhani, & Zlotkin, 2007). Another study by Mannion, Gray-Donald, and Koski (2006) involving milk consumption during pregnancy supports the important role milk and Vitamin D has on the health on the newborn. More recently, maternal vitamin D status and childhood bone mass were correlated in a longitudinal study in the United Kingdom. Mothers with low 25(OH)D concentrations had children with lower bone mineral density at age nine (Javaid et al., 2006).

Birth weight. Mothers with pre-eclampsia during their pregnancy or those with small for gestation babies have been associated with lower concentrations of insulin-like growth factor (IGF-1). Speckler (1994) has further indicated that if women restrict their milk intake, they are at a greater risk of decreased vitamin D and calcium levels, in addition less weight gain in the third trimester of pregnancy. Vitamin D is an important regulator of fetal growth. It increases fetal weight in infants whose mothers are hypocalcemic (Mannion , Gray-Donald, Koski, 2006) and improves maternal and fetal plasma concentrations of 25-hydorxycholecalciferol. Low sunlight, failure to supplement, and poor vitamin D intake leading to low birth weight babies is further supported in Scholl and Chen's study (2008) of 2251 low income pregnant women in Camden, New Jersey; mothers who consumed less than 200 IU/day of Vitamin D had lower birth weight babies.

Cesarean section. Recent studies are indicating vitamin D plays a role in muscle function and may be partially contributing to the cesarean section rate (Ward et al., 2009). In a report by the March of Dimes and published in AORN (Association of Operating Room Nurses) cite an increase of singleton premature cesarean birth deliveries by 10%. Late preterm births at 34-36 weeks gestation accounted for most of the increase in number and rate of cesarean section (March of Dimes, 2008). The United States is the 4th leading country for cesarean sections (behind only Italy, Mexico, and Korea), with one of every three deliveries being a c-section. In 1970, the c-section rate was 5.5%. Today the rate is over 30%, a rate according to the World Health Organization (WHO), is far above the recommended guideline of a 10-15% (Centers for Disease Control, 2008; Leeman, 2008).

Anne Merewood, an assistant pediatrics professor at Boston University School of Medicine concluded in her study that women with low vitamin D levels had a four times greater

risk of cesarean delivery, further stating: "Vitamin D is definitely involved in muscle strength…. contractions of the uterus [which is made of smooth muscle] may not be performing as well as they could be." (Merewood, Menta, Chen, Bauchner, & Holick, 2009).

Pre-eclampsia. For over a decade, large randomized studies have been done to help find an effective treatment for pre-eclampsia. Initial hypotheses looked at the role aspirin played in preventing pre-eclampsia (30,000 patients in 30 trials). Then a study was done involving calcium (15,000 patients in 12 studies). The more recent study published in *Lancet* looked at anti-oxidants, 1000mg vitamin C and 400 IU of vitamin E. The results showed the treatment group presenting symptoms on average eight days earlier than the control group. Apgar scores were lower, birth weight lower, higher rates of cord-blood acidosis, and more unexplained deaths (Lindheimer & Sibai, 2006). These authors discuss how little is known about this sometimes fatal disease in pregnancy, the need for further research, and the need to use caution with vitamin supplements, even at recommended doses. Other studies have supported the possibility of an inflammation process causing pre-eclampsia (Catov, Bodnar, Ness, Markovic, & Roberts, 2007; Goldberg, Hauth, & Andrews, 2000). As more information becomes available, it becomes clear that vitamin D may play a part in preventing infection, and perhaps decreasing the incidence of preterm delivery and pre-eclampsia.

Supporting the need for adequate vitamin D levels during pregnancy is a study from Norway evaluating over 23,000 nulliparous women, finding supplementing with 600-800 IU of vitamin D decreased the incidence of pre-eclampsia by 27 percent. The authors noted no correlation with diet.

Future Research

More data is critically needed to develop safe, effective doses for women prior to and during pregnancy. It is known that obesity plays a role in adverse birth outcomes and that obese women have lower vitamin D levels. Studies need to be done involving the benefits of vitamin D supplementation for pregnant women of varying ages and ethnicity. Education is also necessary to inform providers of the risk groups, diagnosis, treatment, and current research involving vitamin D deficiency. With so many potential benefits to its credit, it becomes imperative that research continue, both to further detect if Vitamin D is effective for improving pregnancy outcomes and also to determine a safe, effective, therapeutic dose.

As more quality research is completed, the hypothesis of vitamin D adversely affecting birth outcomes will either be proven or disproven, however at this stage research is lacking large random experimental studies that would provide the evidence that could change perinatal healthcare practices. In the meantime, healthcare providers are advised to follow research in process, make recommendations to patients based on current research, order 25(OH)D levels on their patients and supplement as needed.

The Institute of Medicine has been evaluating the current vitamin D and calcium recommendations and will make a statement May 2010. Changing recommendations for treatment is an in-depth and lengthy process. Several meetings have been held; the last being closed to the public. Experts from the field of vitamin D research have shared their knowledge, presented to the panel, and assisted in the development of evidence based practice guidelines regarding treatment of vitamin D deficiency. Pregnant women have not been the focus of the recent evaluations or research. However, hopefully with upcoming changes in the general population, pregnant women and children will be the next logical group to be studied.

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