Information about the Critically Appraised Topic (CAT) Series

The objective of the Doctor of Nursing Practice (DNP) program at George Mason University is to prepare graduates for the highest level of nursing practice. Emphasis is placed on evaluating and applying the evidence that supports practice, understanding and creating practice delivery systems based on patient outcomes, and assuming leadership roles in practice settings. Graduates of the program will be able to assume many roles in the health care system, including direct patient care, clinical nursing faculty, practice management, and policy development.

All DNP students take an evidence-based practice course titled Evidence Based Practice in Nursing and Healthcare (NURS 883). This hallmark course for the DNP program builds on knowledge of research methodologies to analyze the selection and evaluation of research underlying evidence based practice. Emphasis is placed on the translation of research in practice, the evaluation of practice and the improvement of the reliability of health care practice and outcomes.

The first assignment students complete is a Critically Appraised Topic (CAT). CATs are mini-systematic reviews and considered a snapshot of the literature on a topic of interest. Students critically appraise literature related to a focused clinical question and summarize the best available research evidence on the topic of interest. CATs conclude with clinical bottom lines for practitioners to quickly take away for consideration in practice.

The CATS published in MARS (Mason Archival Repository Service; mars.gmu.edu) are submitted by students after they have been reviewed, revised, and approved by their instructor. All CATs are current at the time of original publication but will not be updated over time.

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Is increased vitamin D supplementation during pregnancy for deficient and non-deficient mother associated with positive pregnancy/neonatal outcomes?

Purpose: To find out if supplementation of Vitamin D in pregnant women has positive pregnancy and neonatal outcomes.

Appraised by: Huma Hussain

Date of completion: June 20, 2013

Date of review: June 10, 2013

Question: Is increased vitamin D supplementation during pregnancy for deficient and non-deficient mother associated with positive pregnancy/neonatal outcomes?

Search Strategies and Results: EBSCO HOST search engine was used to search: CINAHL (7 articles), MEDLINE (17articles), and PubMed (14 articles) databases. MESH terms used in search: "vitamin D supplementation AND pregnancy AND neonatal outcomes".
There were a total of 8 RCT's from this search, however 5 of these had information irrelevant to the topic being appraised and did not meet MESH term criteria. The three articles chosen were relevant to the topic and of the highest level of evidence, randomized control trials studies.

Chosen Articles:

1. Hollis, B.W., Johnson., D., Hulsey, T.C., Ebeling, M., Wagner, C.L. (2011). Vitamin D supplementation during pregnancy: double blind, randomized control trial of safety and effectiveness. *Journal of Bone and Mineral Research, 26(*10*),* 2341-2357.
2. Roth, D.E., Abdullah, A.M., Raqib, R., Akhtar, E., Perumal, N., Pezzak, B., Baqui, A.H. (2013). Randomized placebo-controlled trial of high dose prenatal third trimester vitamin D3 supplementation in Bangladesh: the AViDD trail. *Nutrition Journal, 12* (47*),* 1-16*.*
3. Wagner, C.I., McNeil, R., Hamilton, S.A., Winkler, J., Cook, C.R., Warner, G., Bivens, B., Davis, D.J., Smith, P.G., Murphy, M., Shary, J.R., Hollis, B.W. (2013). A randomized control trial of vitamin D supplementation in 2-community

health center networks in South Carolina. *American Journal of Obstetrics and Gynecology, 208* (137) e1-13.

Evidence Retrieved:

Hollis et al: 502 consented to participate in this study and were randomly assigned to a treatment group: 166 were assigned to group 1 (400-IU group), 167 were assigned to group 2 (2000-IU group), and 169 were assigned to group 3 (4000-IU group). Of the 502 women enrolled, 350 continued until delivery and 129 exited. Mean 25(OH)D concentrations by group at delivery and 1 month before delivery were significantly different ($p<0.0001$), and the percent who achieved sufficiency was significantly different by group, greatest in 4000-IU group *(*$p<0.0001$). The relative risk (RR) for achieving a concentration of 80 nmol/L or greater within 1 month of delivery was significantly different between the 2000-IU and the 400-IU groups (RR**.**1.52, 95% CI 1.24–1.86), the 4000-IU and the 400-IU groups (RR**.**1.60, 95% CI 1.32–1.95) but not between the 4000-IU and 2000-IU groups (RR**.**1.06, 95% CI 0.93–1.19). Circulating 25(OH)D had a direct influence on circulating 1,25(OH)2D3 concentrations throughout pregnancy *(* $p<0.0001$), with maximal production of 1,25(OH)2D3 in all strata in the 4000-IU group. Neonatal 25(OH)D was significantly correlated with maternal 25(OH)D overall, 1 month prior, and at delivery; 31 of 78 (39.7%) neonates in the 400-IU group, 53 of 91 (58.2%) in the 2000-IU group, and 66 of 84 (78.6%) in the 4000-IU group had a cord blood/neonatal 25(OH)D level in the sufficient range *(*$p<0.0001$).

Appraisal:

Strengths-The study used stratified blocked randomization by ethnicity and balanced enrollment. All subjects were monitored for hypervitaminosis D. The analysis was conducted as an intention to treat. This approach was used a measure of the effectiveness of increasing vitamin D levels via oral dosing. In terms of neonatal vitamin D status by treatment group there was a significant difference among the groups.

Weakness- The study was conducted in southern latitude and therefore vitamin D requirements of women living at more northern latitudes could be greater. Women with preexisting HTN and DM were excluded from the study however these would be at greater risk of deficiency and would receive greater benefit from supplementation. There were a total of 129 women who exited the study, of which 23 had a pregnancy loss and 21 moved away and could not complete the study.

Roth et al: In this study 160 women in Dhaka, Bangladesh were randomized by 1:1 allocation to one of two parallel intervention groups; placebo (n = 80) or 35,000 IU/week of vitamin D3 (n = 80) until delivery. All participants, study personnel and

study investigators were blind to treatment allocation. Mean maternal 25(OH)D concentration was similar in the vitamin D and placebo groups at baseline (45 vs. 44 nmol/L; p = 0.66), but was significantly higher in the vitamin D group vs. placebo group among mothers at delivery (134 vs. 38 nmol/L; p < 0.001) and newborns (cord blood: 103 vs. 39; p < 0.001). In the vitamin D group, 95% of neonates and 100% of mothers attained 25(OH)D >50 nmol/L, versus 21% mothers and 19% of neonates in the placebo group. 95% of newborns had a cord maternal 25(OH)D ratio of 0.5 to 1.5 suggesting that universal maternal prenatal 25(OH)D > 100 nmol would ensure that nearly all cord concentrations are above 50 nmol.

Appraisal:

Strengths: This was a double-blinded randomized control study. There is a strong correlation between maternal delivery and cord 25(OH)D (Pearson correlation=0.87, $p < 0.001$) yet there was substantial variability among mother infant pairs with respect to the cord to maternal ratio. As with the previous study there was no evidence of vitamin D toxicity in participants.

Weakness: This was a small sample size. The enrollment was limited to healthy women at low risk of pregnancy complications, and who were most likely to adhere to the protocol therefore generalizability of findings may be limited. The enrollment period also occurred during a period when vitamin D status was declining from its summer peak. Calculations were not made for total intake of vitamin D due to lack of inadequate information regarding vitamin D content in food supply.

Wagner et al: This study took place in 2 community health centers in South Carolina. 148 participants were to be enrolled in the study with 74 participants per supplementation arm. The majority of women being recruited in this study were either African American or Hispanic, with darker pigmentation and a greater likelihood of vitamin D deficiency. Based
on this initial 25(OH)D level, the randomization was made to 2 groups of 2000 or 4000 IU/d of vitaminD3 was stratified using a cut point of 32 ng/mL. Maternal 25(OH)D (n=161) increased from 22.7 ng/mL (SD 9.7) at baseline to 36.2 ng/mL (SD 15) and 37.9 ng/mL (SD 13.5) in the 2000 and 4000 IU groups. Mean cord blood 25(OH)D was 22.1 +/- 10.3 ng/mL in 2000 IU and 27.0 +/-13.3 ng/mL in 4000 IU groups ($p = .024$).

Appraisal:

Strengths: Women receiving daily doses of 2000 and 4000 IU did not differ in their pre delivery vitamin D status; however, 4000 IU/d was superior to 2000 IU/d in raising maternal vitamin D status over time and in achieving neonatal vitamin D sufficiency, and was associated with lower maternal iPTH. Secondary analyses did show a dose dependent effect with respect to preterm labor, preterm birth, and risk of infection. Neither the 2000IU

nor the 4000IU arms of the study were there any episodes of hypercalciuria or hypercalcemia.

Weakness: In this study there was a non-adherence to protocol of some participants, and also the sample size was small. The decline in 25(OH)D during the last trimester possibly due to increased conversion to 1,25(OH)2D may also reflect the dropout of participants during the pregnancy. This study was not designed as an equivalence study but rather to demonstrate superiority of one dose over the other.

Conclusion/Clinical Bottom Line: The findings suggest that the current vitamin D estimated average requirement and recommended dietary allowance for pregnant women issued in 2010 by the IOM should be raised to 4000 IU of vitamin D per day so that all women, regardless of race, can attain optimal nutritional and hormonal vitamin D status throughout pregnancy. Supplementation in the third trimester alone of pregnancy with vitamin D 5000IU daily also significantly raises maternal and cord serum 25(OH)D concentrations above 50 nmol. The nutritional vitamin D status of the neonate is completely dependent on the vitamin D stores of the mother. Maternal supplementation with vitamin D during pregnancy improves maternal/neonatal vitamin D status. Studies suggest that supplementation of vitamin D at these level poses no increase risk of hypercalcemia or other observed safety concerns.