A Call to Action: Pregnant Women In-Deed Require Vitamin D Supplementation for Better Health Outcomes

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In a recent issue of the *Journal of Clinical Endocrinology and Metabolism*, Rostami *et al.* (1) report on a study evaluating the effectiveness of a prenatal screening program for optimizing vitamin D status (serum 25-hydroxyvitamin D [25(OH)D]) during pregnancy. They related the outcome of this program to the prevention of pregnancy complications. They observed a >25-fold increase in the number of pregnant women who were able to achieve a 25(OH)D that was >20 ng/mL when they were screened for their vitamin D status and provided vitamin D supplementation compared with pregnant women who were not screened and therefore were not advised to take a vitamin D supplement. They observed a remarkable decrease in adverse pregnancy outcomes for women who were screened and received vitamin D supplementation. These included some of the most serious adverse complications during pregnancy, including 60%, 50%, and 40% decreases in preeclampsia, gestational diabetes, and preterm delivery, respectively. This commentary begins with a brief summary of previous studies, providing insight about the controversy associated with vitamin D supplementation recommendations prior to discussing this meritorious study and its health implications for pregnant women and their newborns.

There continues to be controversy regarding what the circulating levels of 25(OH)D should be for maximum health. The Institute of Medicine (now the National Academy of Medicine) recommended that all children >1 year of age and all adults up to 70 years of age require 600 IU of vitamin D daily to maintain a blood level of 25(OH)D of at least 20 ng/mL (2). A retrospective study of 40 mother/infant pairs who were documented to have ingested ~600 IU of vitamin D a day (prenatal vitamin containing 400 IU of vitamin D and an average of 2.3 classes of milk daily containing 230 IU of vitamin D) throughout their pregnancy, 50% of the mothers and 65% of the infants had a circulating level of 25(OH)D of <12 ng/mL at the time of birth. When using a circulating level of 25(OH)D <20 ng/mL as the cutoff, 76% of the mothers and 81% of the newborns were vitamin D deficient (3).

The study of Rostami *et al.* also found that preterm delivery was not only associated with vitamin D deficiency but that there was an indirect relationship with blood levels of 25(OH)D and increased risks. Women who had blood levels of 25(OH)D <10 ng/mL and received vitamin D supplementation decreased the risk of preterm delivery by 67%, and those who had levels between 11 and 20 ng/mL had a 30% decline in premature births. These data are consistent with the *post hoc* analysis by Wagner *et al.* (4) They not only demonstrated a 59% decrease in premature delivery in women who had blood levels of 25(OH)D >40 ng/mL compared with women who had blood levels <20 ng/mL, but they also reported less of a decrease for those women who maintained a blood level of 20 to 40 ng/mL [41% vs 59% in women with a 25(OH)D >40 ng/mL]. Equally impressive was the observation when taking into account all three adverse outcomes (*i.e.*, preeclampsia, gestational diabetes mellitus, and preterm delivery), women who were screened and treated for the vitamin D deficiency decreased the odds of these adverse events by 55%.

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Abbreviation: 25(OH)D, 25-hydroxyvitamin D.

As significant as these observations are for the health of pregnant women and their newborns, vitamin D deficiency *in utero* has long-lasting negative health consequences for susceptibility of developing chronic debilitating illnesses in adult life (5). Epigenetic fetal programming as a result of environmental events during pregnancy induces specific genes and genomic pathways that not only control fetal development but also subsequent disease risk (4). The placenta has the capacity, similar to the kidneys, to convert 25(OH)D to its active form, 1,25-dihydroxyvitamin D (5). This hormonal form of vitamin D is known to modify histones by inducing their acetylation (5). It has been suggested that histone modifications have long-lasting consequences on the genomic activities of 1,25-dihydroxyvitamin D (5–7). This effect is not only on calcemic actions but also on noncalcemic actions, including immunomodulation with the attendant decrease in autoantibody production and antimicrobial peptide gene activation (5, 8). This may help explain associations with vitamin D deficiency *in utero* and in infancy with increased risk for autoimmune diseases, including multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and Crohn disease in childhood and later in life (5, 9). Infants born of mothers who were vitamin D deficient are also more likely to have wheezing disorders early in life (9).

The authors used a somewhat complex methodology in their prospective study design. It was not a classic randomized controlled study because the study was conducted in two separate sites that were not randomized, as participants at one site and those from the other site with blood levels of 25(OH)D >20 ng/mL were considered as the control group. They instituted a treatment schedule for vitamin D deficiency based on the baseline screened levels of 25(OH)D. It would seem intuitively obvious that patients who have severe vitamin D deficiency [*i.e.*, 25(OH)D <10 ng/mL] would require higher doses of vitamin D than patients with a blood level of 10 to 20 ng/mL to correct their vitamin D deficiency. This, however, turns out to be incorrect, as was also appreciated by Rostami *et al.* (1) There are several vitamin D 25-hydroxylases in the liver that have different affinities and Michaelis constants (substrate concentration at one half the maximum velocity) for vitamin D. As a result, regardless of whether the patient is severely vitamin D deficient or moderately vitamin D deficient, giving them the same amount of vitamin D will achieve a similar blood level of 25(OH)D (9, 10). The maximum change for a given dose occurs ~6 to 8 weeks after initiating the therapy. Once a blood level of 25(OH)D reaches the threshold of ~20 ng/mL then 100 IU of vitamin D will increase blood level by ~1 ng/mL (11).

There has been concern by obstetricians and pediatricians that high doses of vitamin D during pregnancy can increase risk for birth defects and neonatal hypercalcemia (12). This study again demonstrates that there should be little concern about giving doses of 50,000 IU weekly for up to 12 weeks or a dose as high as two doses of 300,000 IU intramuscularly. This is especially important for patients who may only be seen infrequently or once during their pregnancy. The preferred route, however, is the oral administration of vitamin D. What still needs to be determined is how much vitamin D is required during pregnancy to achieve a blood level of 25(OH)D >20 ng/mL, which decreased pregnancy adverse outcomes (1). Although it is unlikely that 600 IU of vitamin D daily can achieve these levels (3), studies are needed to determine the minimum amount of vitamin D requirements during pregnancy to achieve blood levels of 25(OH)D >20 ng/mL. Hollis and colleagues (12) had reported that 4000 IU of vitamin D daily throughout pregnancy not only corrected vitamin D deficiency but maintained serum blood levels of 25(OH)D in the range of 40 to 50 ng/mL without any evidence of hypercalciuria or hypercalcemia.

The results from this study are monumental when considering all of the health care ramifications and health care costs associated with the three most serious complications of pregnancy. If a pharmaceutical company had developed a drug to reduce risk by even 10% they would have a multibillion dollar business. The cost associated with correcting and preventing vitamin D deficiency is miniscule when compared with a newly developed medication. Should we be screening all pregnant women for their vitamin D status? This is problematic at several levels, including the availability of a reliable test to determine the blood level of 25(OH)D as well as the cost. It is much more cost-effective to give all pregnant women vitamin D supplementation. How much is still not well established. Six hundred IU daily was not demonstrated to be effective in achieving a 25(OH)D of at least 20 ng/mL (3). A daily intake of 1500 to 2000 IU or its equivalent, as recommended by the Endocrine Society, will achieve the desired level of a 25(OH)D of at least 20 ng/mL. Whether taking 4000 IU daily and raising blood levels of 25(OH)D to >30 ng/mL during pregnancy provides additional benefits requires further investigation. Vitamin D supplementation should be a required standard of care recommendation for all women, especially women of childbearing age and those who are pregnant.

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