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Review

Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: A combined analysis☆

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ABSTRACT

Objective: To assess the safety and health effects of vitamin D supplementation during pregnancy.
Methods and design: Datasets from two randomized clinical trials were first analyzed separately then combined for this analysis using a common data dictionary. In the NICHD trial, women were randomized to 400, 2000, or 4000 IU vitamin D_3/day, stratified by race. In the Thrasher Research Fund trial, participants were randomized to 2000 or 4000 IU vitamin D_3/day. Study drugs were from the same manufacturing lot for both trials. Identical questionnaires were given for comparable sociodemographics & clinical characteristics. Outcome measures were: [1] maternal and neonatal 25(OH)D achieved, and [2] maternal comorbidities of pregnancy (COP). SAS 9.3 was used for all analyses.
Results: In the combined cohort, there were 110 controls, 201 in the 2000 IU group, and 193 in the 4000 IU group. No differences between groups in baseline 25(OH)D were found; however, delivery and cord blood values were greater in the 4000 IU group ($p < 0.0001$), an effect that persisted even after controlling for race and study. A greater percent were vitamin D replete in the 4000 IU group ($p < 0.0001$). There was a trend where the 4000 IU group had decreased rates of comorbidities of pregnancy. There was a strong association between COP and final maternal 25(OH)D; an effect that persisted even after controlling for race and study ($p = 0.006$).
Conclusions: Supplementation with 4000 IU/day was associated with lower risk of hypovitaminosis D than Control and 2000 IU groups. While not statistically significant, there was a trend toward lower rates of COP as supplementation dose increased. Maternal delivery 25(OH)D was inversely associated with any comorbidity of pregnancy, with fewer events as 25(OH)D increased. Future studies are needed to confirm these findings and determine the mechanisms of action of such effects.
This article is part of a Special Issue entitled 'Vitamin D Workshop'.

Contents

Abbreviations: NICHD, National Institute of Child Health and Human Development; TRF, Thrasher Research Fund; 25(OH)D, total circulating 25-hydroxy-vitamin D.

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1. Introduction

It is clear that vitamin D status during pregnancy varies around the globe as a function of maternal sunlight exposure, degree of skin pigmentation, latitude, lifestyle, body mass index (BMI) and the intake of oral vitamin D supplements [1–8]. It is common knowledge that if a woman is deficient during her pregnancy, then her fetus also will be deficient during gestation [1,9]. Whether such variation in vitamin D status can be associated with worse pregnancy outcomes still remains an open question.

While studies conducted in the 1980's and 1990's gave some evidence that maternal deficiency was associated with abnormal fetal growth, dentition and maternal health, there were issues with these studies as they were conducted with small sample sizes and the amount of vitamin D given was often low with few differences noted between women who had received placebo and those who had received treatment – typically 400 IU vitamin D/day [10–14]. Prior studies did not establish the optimal vitamin D requirements and blood levels during pregnancy. More recently, larger doses up to 10,000 IU/day in nonpregnant adults have been found to be safe [15–18] and such higher dosing necessary to achieve sufficiency in certain individuals. Yet, whether these findings are applicable to the pregnant woman has not been fully addressed.

To begin to answer the question of what constitutes vitamin D sufficiency during pregnancy, two recent randomized clinical trials conducted by our group were presented and published [1,19]. The largest was an NICHD-sponsored randomized controlled trial of vitamin D supplementation beginning at 12–16 weeks of gestation where healthy women were randomized to one of three treatment groups – 400, 2000, and 4000 IU vitamin D_3/day [1]. In the second clinical trial sponsored by the Thrasher Research Fund, women were randomized at 12–16 weeks of gestation to either 2000 or 4000 IU vitamin D_3/day [19]. Vitamin D status and health characteristics were recorded for both studies. Because both studies were conducted concurrently by the same study team using a common data dictionary, the datasets were combined to increase sample size and to collectively address the following questions: [1] what are the potential health effects of vitamin D_3 supplementation during pregnancy, and [2] what are the implications of vitamin D deficiency on the mother and her fetus?

2. Methods and experimental design

Datasets from the NICHD and Thrasher Research Fund vitamin D_3 supplementation trials were combined for this analysis using a common data dictionary. In the NICHD trial, (as shown in Fig. 1A), women were randomized to a total of 400, 2000 or 4000 IU vitamin D_3/day, stratified by race with supplementation beginning between 12–16 weeks of gestation [1]. In the Thrasher Research Fund (TRF) trial (see Fig. 1B), after an initial run-in dose of 2000 IU/day for 1 month, participants were randomized to total of either 2000 or 4000 vitamin D_3/day, stratified by race [19]. Details about both clinical trials have been published previously [1,19] and are summarized below. All participants received study drugs from the same manufacturing lot. The studies administered identical questionnaires to produce comparable sociodemographic/clinical characteristics using the same criteria.

Outcome measures for both clinical trials included the following: [1] maternal baseline and delivery 25(OH)D; [2] neonatal 25(OH)D concentration; [3] comorbidities of pregnancy (gestational diabetes, preeclampsia, hypertensive disorders of pregnancy; any infection; bacterial vaginosis (BV); preterm birth without preeclampsia as defined by an obstetrician).

2.1. Study design of NICHD trial

This study was a single-center, randomized controlled, double-blinded study of vitamin D supplementation (FDA IND #66,346; ClinicalTrials.gov #NCT00292591) approved by MUSC's Institutional Review Board for Human Research (HR#10727) [1]. Women

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