Preventing Health Disparities during Pregnancy through Vitamin D Supplementation

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Statistical Analysis: The primary analysis in this investigation will compare levels of maternal 25(OH)D across the two supplementation groups as 'Intention-to-Treat' and will employ Mantel-Haenszel mean scores; however, a 'Per Protocol' (oversampling to consider attrition) analysis also will be done. This two-step analysis provides information regarding the efficacy of these dosage levels in increasing vitamin D and the effectiveness of oral supplementation to increase vitamin D. Whether the losses are random or are biased with respect to ethnicity, or supplementation arm will be tested. Any differential losses will be reported and examined with the use of propensity scores.

Because of the unique nature of the contributions of potential confounders, two approaches to the analysis will be employed. The first and primary analysis will use a Mantel-Haenszel estimate of the mean treatment difference, computed from stratum-specific treatment differences, which will utilize a weighted average of treatment differences across ethnicity. Mean differences will be calculated for the experimental dosage relative to the 400 IU group. Bonferroni adjustments will be made for the Type I per comparison error rates to correct for multiple testing. The treatment differences, estimated variances, and confidence intervals for the differences will be estimated for maternal serum 25(OH)D. This mode of analysis is quite effective in clinical trials as it is less dependent on normal theory assumptions and associated assumptions such as homogeneity of variance. Parametric models also will be fit, but the primary analysis will rest on Mantel-Haenszel mean scores techniques readily done within SAS. Parametric dose response curves also will be generated to describe the relationship between 25 (OH)D and dosage.

The proportion of participants who completed the daily supplement regimen will be estimated, with a similar "per protocol" style analysis restricted to those individuals. Finally, techniques of multiple linear regression will be employed to describe the interactive effects of ethnicity, as well as the effects of other covariates, such as seasonality, mother's age and fecundity, on baseline serum 25(OH)D. These models will be assessed for violations of the model assumptions, and corrected for such violations as appropriate.

The second statistical approach measures the effects of the confounders and takes the more traditional approach of assuming normal distribution for Vitamin D, and will be performed in parallel fashion to compare treatment effects in 400 IU and 4400 IU vitamin D groups. The primary research aim is to determine if supplementation is associated with an increase in vitamin D concentrations. As discussed below, it will be necessary to identify and control for other factors (confounders) that may also be associated with changes in vitamin D levels.

Paired analyses according to the study plan will be conducted by employing McNemar chi-square for categorical variables, paired t-tests for normally distributed variables, repeated measures ANOVA for longitudinal analyses, and multiple linear regression for multi-variable analyses to control for confounding. Correlation will be used to assess the linear association between outcomes and those factors expected of an accumulated dose-response relationship (e.g., sunlight exposure), and individual regression tests to identify the strength of the association between outcomes and each characteristic. The resulting coefficients then will be translated into

a formula for the linear association between each factor and outcomes. In the event that there are non-linear distributions, appropriate data transformations will occur as necessary.

Both groups will be compared for differences in any factors at baseline, and will include: information contained in the maternal sociodemographic, maternal pregnancy and delivery, and maternal calcium, creatinine, vitamin D_3, 25(OH)D, and urinary calcium creatinine ratio. While the stratified blocked randomization technique should minimize the potential for baseline differences, this first step will confirm whether there should be adjustment for any initial differences in follow-up analyses. Next, differences between baseline and follow-up will be examined for those variables that may have changed over the follow-up period (health assessment; physical activity; and blood and urine outcome measures) to identify those factors that may serve as confounders or effect modifiers for the vitamin D assessments. The potential influence of identified confounders or interaction terms will have to be considered for any change in vitamin D status.

Changes in vitamin D outcomes will be compared between treatment arms with the additional information from sunlight exposure, pigmentation/melanin index, maternal physical activity assessment, maternal dietary history, health, and medication questionnaires. This detail will allow the separation of changes in vitamin D parameters as a function of confounding factors from supplementation. The study is powered to explore the degree to which changes in vitamin D parameters are a function of supplementation and ethnicity. To assess whether there are differences in the slopes or linear dissimilarities in the outcomes over time, repeated measures techniques will be used to compare longitudinal changes in outcomes between groups. This technique also provides a graphical depiction of the slopes over time and can identify if there are linear or plateau responses to differences in vitamin D supplementation concentration; it also will allow determination of data transformation techniques required for subsequent analyses if the slopes over time are non-linear.

The final step in the second statistical approach will determine whether potential group differences in the various outcomes are a function of any of the potential confounders—with particular attention to skin pigmentation and sunlight exposure. This step will identify changes in outcomes associated with population factors independent of the group (supplementation) assignment. The extent of more complex statistical analyses will be predicated on the number of individuals comprising specific strata, and thus, restricted by a reduction in the statistical power. Such comparisons will be reported as information for future studies. To clarify, using sunlight exposure as a representative example, the independent effect of vitamin D supplementation may be found to have been modified by the amount of sunlight exposure. As such, the changes in outcomes attributable to each factor, independently, and then when considered in combination will be partitioned. While the major goal of this study is to examine the various outcomes as an independent function of vitamin D supplementation—thereby controlling for all other group differences, the changes in outcomes that are associated with these group differences will be examined and reported in detail. In this way, the changes in vitamin D that are associated with each factor independently will be partitioned.