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Can we prevent Childhood Asthma Before Birth: Summary of the VDAART results so far

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Abstract

When VDAART was launched we assumed the effects of vitamin D were confined to the alveolar stage of lung development i.e. the third trimester. Fetal lung expression data and a demonstration that vitamin D influenced early fetal lung development emerged after the trial was under way. Finally, initial level of vitamin D at trial entry misclassified subjects at entry to the trial. Initial nutrient level is an important modifier of trial response in VDAART and intent to treat analyses stratified by initial level show a greater effect of vitamin D than iwasseen when initial level is not accounted for.

In 2004 we identified the Vitamin D receptor as a gene for asthma(1). This suggested to us that vitamin D itself might play a role in the development of the disease. There were two ways that we could have gone to try and test this hypothesis. We could have investigated the molecular genetics of the vitamin D pathway or we could have sought more epidemiologic evidence for an association between vitamin D intake in the mother and asthma in the child.

We chose the latter course and performed two prospective cohort studies to assess total vitamin D intake during pregnancy and the risk of asthma in the offspring of these mothers(2, 3). Both studies suggested that mothers with the highest intake of vitamin D had about a 40% decrease in asthma incidence in their offspring compared to mothers in the lowest quintile (quartile). These data strengthened our suspicion that the observed association might be real but we knew that we would need to perform a clinical trial to assess this association more directly.

We developed our theory as to how vitamin D deficiency in pregnant women might be responsible for the observed increase in asthma incidence from 1970–2000 and that this deficiency fit the characteristics of the epidemic well, including the greater severity in the inner city and among African American subjects(4). We also reviewed data on the effects of vitamin D on the developing lung and fetal immune system. We wrote, and were subsequently awarded, an R01 from NHLBI to investigate this hypothesis(5). The design of the study was straightforward. We randomized women at high risk of having an asthmatic child; e.g. they, or their family members, had asthma and allergies to one of two treatment groups: 4000 IU of vitamin D/day plus a multivitamin containing 400 IU or placebo plus a

Declaration of interest

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multivitamin containing 400 IU of vitamin D. Women were enrolled in the trial between the 10–18 week of pregnancy and were followed through their pregnancy and the children were followed until age 3(5).

A total of 881 women were randomized at three clinical centers. The aims of the trial were to test the dose of 4400 IU of vitamin D and see how many women were raised to “sufficient “ levels defined as > or = to 30 ng/ml (75ug/L). The second aim was to see if we could decrease asthma in the offspring of the women by 40% as we had seen in the observational studies. Vitamin D levels were measured in the women at entry into the trial (10–18 weeks of gestation) and at the third trimester of pregnancy (32–38 weeks of gestation).

The trial ended its first phase in 2014 and the initial intent to treat results were published in JAMA in January of 2016. Firstly, only 75% of women had their vitamin D levels raised to the “sufficient threshold. This is probably because of the high number of African American women in the trial who started at very low initial levels of vitamin D at entry to the trial and the dose of 4400 IU of vitamin D was not sufficient to raise their levels into the sufficient range. Second, the effect of vitamin D on asthma/wheeze outcome was a 20% reduction in asthma risk in the offspring not the hypothesized 40% that we saw in the observational studies, and as a result of this reduced effect, the results were of only borderline statistical significance (p=0.051) (6). What happened?

Three separate methodological issues conspired to minimize the effects seen in the intent to treat analysis of the trial data. First, when the trial was funded and launched, we had assumed that the effects of vitamin D were confined to the alveolar stage of lung development that occurs in the third trimester of fetal development(4). However, after the trial was already designed and under way, we undertook a study of fetal lung gene expression, that suggested that vitamin D had effects at the stage of branching morphogenesis of the lung that occurs as early as the first trimester namely at the time of randomization(7). Thus targeting women at the 10–18 weeks of pregnancy was probably too late for this early pregnancy effect of vitamin D on lung development.

Second, there is a growing body of evidence that in many species, including man, vitamin D is critical to implantation of the fertilized egg in the wall of the uterus and that human fertility is, in part, controlled by vitamin D again suggesting that early pregnancy levels of vitamin D are deterministic for the effects of vitamin D on pregnancy outcomes, including those related to lung development(8). Again suggesting that we needed to start our trial earlier than 10–18 weeks of gestation.

Finally, as Heaney has noted, there is a growing realization that nutrient trials are unlike drug trials in that there is a level of nutrient on board at the time the trial begins. If the nutrient is critical to the outcome of the trial, variation in nutrient levels at entry to the trial must be accounted for in the trial design(9). When we performed an intent-to-treat analysis, stratified by final level of vitamin D in the trial the results were substantially more statistically significant than the standard intent-to-treat(6). The very low levels of vitamin D at entry in the trial in some women is a powerful factor leading to misclassification of

subjects, a factor that was not accounted for by randomization and hence not accounted for in the intent-to-treat analysis originally reported (6).

We are currently performing additional vitamin D level based analyses to determine which level of vitamin D: the initial level at entry into the trial or the final level or both are the critical values and we feel that once we account for this effect of initial level that then the trial results will be much clearer and easier to interpret.

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