Vitamin D and risk of pregnancy related hypertensive disorders: mendelian randomisation study

BMJ 2018; 361 doi: https://doi.org/10.1136/bmj.k2167 (Published 20 June 2018)

https://www.bmj.com/content/361/bmj.k2167

Abstract

Objective To use mendelian randomisation to investigate whether 25-hydroxyvitamin D concentration has a causal effect on gestational hypertension or pre-eclampsia.

Design One and two sample mendelian randomisation analyses.

Setting Two European pregnancy cohorts (Avon Longitudinal Study of Parents and Children, and Generation R Study), and two case-control studies (subgroup nested within the Norwegian Mother and Child Cohort Study, and the UK Genetics of Pre-eclampsia Study).

Participants 7389 women in a one sample mendelian randomisation analysis (751 with gestational hypertension and 135 with pre-eclampsia), and 3388 pre-eclampsia cases and 6059 controls in a two sample mendelian randomisation analysis.

Exposures Single nucleotide polymorphisms in genes associated with vitamin D synthesis (rs10741657 and rs12785878) and metabolism (rs6013897 and rs2282679) were used as instrumental variables.

Main outcome measures Gestational hypertension and pre-eclampsia defined according to the International Society for the Study of Hypertension in Pregnancy.

Results In the conventional multivariable analysis, the relative risk for pre-eclampsia was 1.03 (95% confidence interval 1.00 to 1.07) per 10% decrease in 25-hydroxyvitamin D level, and 2.04 (1.02 to 4.07) for 25-hydroxyvitamin D levels <25 nmol/L compared with ≥75 nmol/L. No association was found for gestational hypertension. The one sample mendelian randomisation analysis using the total genetic risk score as an instrument did not provide strong evidence of a linear effect of 25-hydroxyvitamin D on the risk of gestational hypertension or pre-eclampsia: odds ratio 0.90 (95% confidence interval 0.78 to 1.03) and 1.19 (0.92 to 1.52) per 10% decrease, respectively. The two sample mendelian randomisation estimate gave an odds ratio for pre-eclampsia of 0.98 (0.89 to 1.07) per 10% decrease in 25-hydroxyvitamin D level, an odds ratio of 0.96 (0.80 to 1.15) per unit increase in the log(odds) of 25-hydroxyvitamin D level <75 nmol/L, and an odds ratio of 0.93

(0.73 to 1.19) per unit increase in the log(odds) of 25-hydroxyvitamin D levels <50 nmol/L.

Conclusions No strong evidence was found to support a causal effect of vitamin D status on gestational hypertension or pre-eclampsia. Future mendelian randomisation studies with a larger number of women with pre-eclampsia or more genetic instruments that would increase the proportion of 25-hydroxyvitamin D levels explained by the instrument are needed.

Reviewer: 1- Patient and Public Reviewer

Comments:
I am a patient that had early onset preeclampsia with no risk factors in 2003. The pregnancy ended with a stillborn baby. I was sick in the hospital for another 7 days after delivery. After my pregnancy, I read all that I could about ways to prevent preeclampsia, and I decided, with information I had at that time and in consultation with my medical team, to not use any supplements (aspirin and Calcium were popular options). In 2005, in a subsequent pregnancy, I had PIH. I delivered at 36 weeks a healthy baby boy. My hypertension increased significantly towards the end of this pregnancy, without any other symptoms or abnormal lab results.

The article is very technical and I will rely on my professional peers to review the data and analysis. Due to my history, this will be an emotional review.

It is difficult to describe the bewilderment that parents affected by preeclampsia and PIH feel when finding out that there are so few ways to prevent these diseases. We feel guilty that we did not eat well enough, or didn't take the right supplements, or didn't manage stress more effectively. We wonder how our doctors didn't tell us more about this disease. We wonder why they did not catch it earlier to "fix" it.
In preparing for a new pregnancy, we research everything that we can do to make a new pregnancy more successful. We read the recommendations from WHO, ACOG and other organizations and we wonder if they are up to date, if they really looked for everything that could help.

Research like this that enforce and expand what we know about the efficacy or non-efficacy of various supplements is very important for women that are thinking about pregnancy and are worried about having a healthy pregnancy. It is important to expand the research and include new ways to study the data for better assurance.
As a patient, the abstract is a very important part of the articles. It is the text that a patient could have access to behind a paywall. The "Conclusions" section is very clear and accessible to patients. The paragraphs "What is already known on this topic" and "What this study adds" are bringing in slightly more information, that could help patients if included in the Conclusions.

I found the "Discussion" section enlightening and I appreciated the additional information included in the WEB APPENDIX.

I hope that the technical aspect of the study is sound and that this article will be published in a similar format. Patients need this information.
I thank the authors for researching this important area and BMJ for inviting me to review and for considering publishing this article.

Additional Questions:
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Job Title: Patient Reviewer/Project Manager
Institution: Dulcian, Inc.
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