PREDIN: Pregnancy and Vitamin D Intervention study – a randomized controlled trial

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INTRODUCTION

Vitamin D deficiency is common among certain risk groups in Sweden. The investigators have shown in the first large Swedish multi-ethnic population-based study, the GraviD cohort, that every tenth pregnant woman in Västra Götaland is vitamin D deficient (<30 nmol/l, 25-hydroxyvitamin D; 25OHD) (1). The prevalence of vitamin D deficiency in pregnancy was two times higher during the winter and five times higher within certain ethnic minorities. Vitamin D insufficiency was also common, as 25% had 25OHD <50 nmol/l. Thus, at northern latitudes many pregnant women are already at risk of vitamin D deficiency and insufficiency. The increasingly multi-ethnic population residing in Sweden makes vitamin D deficiency a growing clinical challenge for society and health care.

The effect of maternal vitamin D in pregnancy for maternal and offspring health needs to be clarified. In observational studies, the investigators and others show associations between poor maternal vitamin D status in pregnancy and increased odds of gestational hypertension and preeclampsia (2), fetal growth restriction (3, 4), and preterm birth (4, 5). Poor maternal vitamin D status is also linked to impaired growth in the first year of life, and potentially also to higher risk of developing obesity in childhood (6). Limited evidence suggest that maternal vitamin D supplementation improve neonatal bone mineral content (7), in neonates born during the winter at the seasonal nadir of vitamin D status. Since the evidence for positive effects of maternal vitamin D status or intake is limited, vitamin D interventions in pregnancy are warranted to clarify the causal effects of vitamin D in pregnancy and the doses required to achieve sufficient vitamin D status in deficient women.

Current recommendations for vitamin D intake in pregnancy

According to the 2012 Nordic Nutrition Recommendations, pregnant women are recommended the same dietary intake of vitamin D as the general adult population; 10 µg/day. For individuals with little or no sun exposure, 20 µg/day is recommended (8).

The national dietary survey Riksmaten from 2010 showed that median vitamin D intake was low at less than 6 µg/day in the overall adult population, and lowest among young women at 4.4-5.1 µg/day (9). The dietary intake of pregnant women is not included in this survey but results from our population based cohort study of pregnant women, show that dietary intake is around 5 µg/day also in this population and that only 6% of women reach the recommended intake through diet alone (10). As a result of the low reported intakes of vitamin D in Sweden,

the mandatory vitamin D fortification policy was extended by the National Food Agency in 2018, to include a wider range of foods and to increase the vitamin D content of fortified products (11). The effect of the new policy on vitamin D intake and status is currently unknown, but our preliminary projection data show that vitamin D intake will likely double in the pregnant population. However, those who do not consume dairy products or margarine will not benefit from the increased fortification and will remain at very low dietary vitamin D intake. Preliminary data from the investigators group show that the ethnic minority groups with high risk of vitamin D deficiency are also at high risk of a continued low vitamin D intake, as they consume less of vitamin D fortified foods. The recommendations for vitamin D intake may therefore be difficult to achieve by diet alone, despite the increased fortification, and supplement use may therefore be warranted for certain groups.

Vitamin D supplementation is recommended for risk groups of poor vitamin D status by the National Food Agency. For adults, the recommendations are to take a daily supplement of either 10 µg if dietary intake or sun exposure is low. If both dietary intake and sun exposure is low, 20 µg/day is recommended (12). There are no specific recommendations for pregnant women, so these recommendations apply also for them.

Are the recommendations sufficient?

There is an increasing body of evidence to suggest that the current recommendations are not sufficient to maintain adequate vitamin D status throughout the year. A 2020 individual participant data meta-analysis show that over 30 µg/day is needed to maintain 25OHD concentration >50 nmol/L during winter, in 90% of the adult population (13). Results also showed that very high intakes (92 µg/day) was required to ensure adequate vitamin D status among >97.5% of the population. These results suggest that the current dietary recommendation of 10 µg/day might be insufficient to maintain optimal vitamin D status for many individuals.

The current recommendations for supplemental vitamin D intake at 10 or 20 µg/day for risk groups, is likely too low to achieve the target levels of 25OHD at >50 nmol/L. One µg/day is assumed to raise 25OHD concentration by 1.2 nmol/L. Thereby, for someone with vitamin D deficiency (i.e. 25OHD <30 nmol/L), 15-40 µg/day would be needed to achieve 25OHD >50 nmol/L, depending on the severity of the deficiency.

SPECIFIC SCIENTIFIC AIMS

The double-blind randomized controlled trial (RCT) will include pregnant women with high risk of vitamin D deficiency. Women will be randomized to one of three groups: usual care, or supplementation with either 20 or 40 µg/day vitamin D/day starting in the first trimester. The PREDIN RCT will be conducted within the antenatal care units in Gothenburg with start in 2021. In addition, the investigators aim to evalute if the overall vitamin D status and vitamin

D intake have increased since the expanded vitamin D fortification program was initiated in year 2020.

The specific aims are to test the hypotheses that:

1. Maternal vitamin D_3 supplementation with 40 µg/day will be more effective than 20 µg/d in achieving vitamin D sufficiency (25OHD ≥50 nmol/l) in pregnant women
2. Maternal vitamin D_3 supplementation (both 20 and 40 µg) during pregnancy will be more effective than usual care in obtaining vitamin D sufficiency (25OHD ≥50 nmol/l) in pregnant women
3. The expanded vitamin D food fortification program has increased the vitamin D status and vitamin D intake of pregnant women in Gothenburg since 2013-2014
4. Vitamin D status and/or vitamin D intake is related to risk of developing complications during pregnancy or delivery

METHODS AND MATERIALS

The PREDIN RCT is a randomized double-blind trial with three parallel arms, providing pregnant women with either usual antenatal care, or a daily pill of 20 or 40 µg/day vitamin D_3 (cholecalciferol), in the first trimester of pregnancy.

Recruitment and allocation

The study will be conducted within the antenatal care in Gothenburg. At a routine visit in early pregnancy, women will receive study information orally and in writing. A signed informed consent is needed to be included as participant in the study. According to clinical praxis, interpreters will be present when needed. In addition, study information will be translated into other languages, e.g. English, Somali and Arabic.

Inclusion criteria for screening for the RCT are age 18-45 years and gestational week <15. Exclusion criteria are multifetal pregnancy, known disorder to the metabolism of vitamin D, calcium or phosphate (e.g. adrenal gland disorders, kidney disease), ongoing treatment with vitamin D of ≥10 µg/day and difficulties understanding the study information.

Included women will be screened for risk of vitamin D deficiency, using a validated screening tool (manuscript under review), and they will be invited to complete the study questionnaires and have blood drawn for later analyses. These data will be used for aim 3 and 4.

Women at high risk of vitamin D deficiency, defined as a screening score ≥15 points, will be randomized to one of the three study arms. Blindness towards both subjects and research staff will be ensured in the two groups receiving vitamin D supplementation. For practical reasons, the group receiving usual care will be open label.

Power for sample size

Power is based on the difference in the primary outcome, proportion of vitamin D sufficiency (25OHD >50 nmol/L) at follow up in the third trimester, between the groups receiving 20 or 40 µg vitamin D per day. Assuming that 50% and 90% achieve vitamin D sufficiency in the respective groups, 17 participants per group is needed. Assuming 50% retention rate, 102 women will be included and randomized to one of the three groups using a computer generated randomization list. To reach the target sample size of 102 women, it is estimated that approximately 500 women will need to be screened. This is based on a 20% prevalence of high risk of vitamin D deficiency according to the screening tool.

Data collection

At screening, data on socio-demographic factors, ethnicity, dietary intake, eye color, sun exposure, and health status (including use of medications) will be collected using questionnaires. Blood will be drawn and banked for later analysis. Women will be followed up in the third trimester of pregnancy, through assessment of dietary intake and blood draw. Compliance and adverse events will be monitored through questions posed by the midwife in the third trimester at the follow-up visit.

Banked blood will be analyzed for 25OHD and other vitamin D metabolites, nutritional biomarkers, inflammation, hormones and gene variants related to vitamin D metabolism.

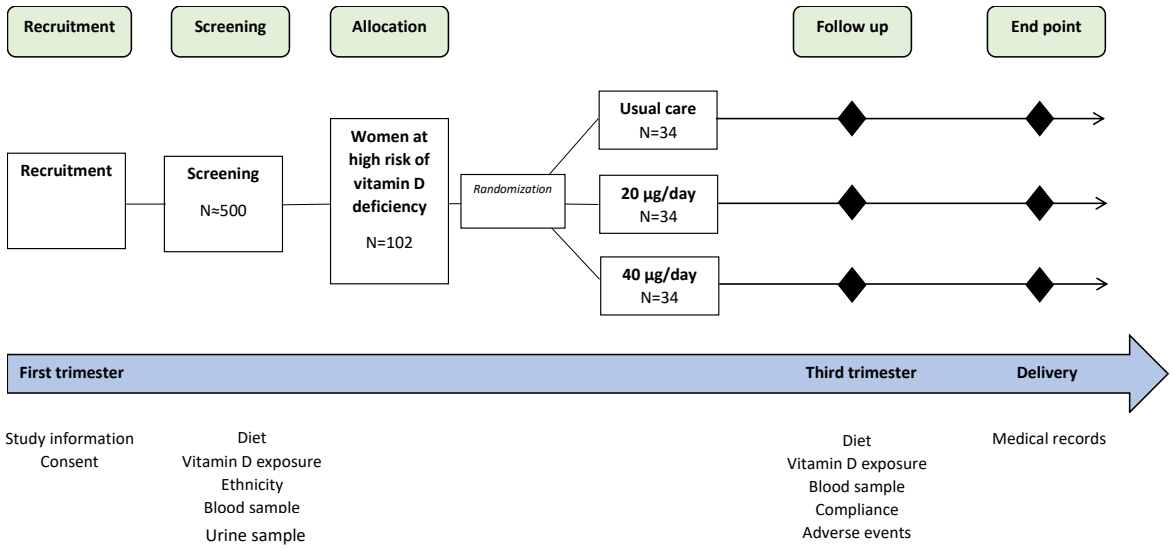

Figure 1. Study design for the PREDIN study

For all women, information on gestational complications, fetal growth and gestational age at birth will be retrieved from medical records via the antenatal care after birth. Retrieved variables for the child will include weight, length, head circumference, vitality signs (Apgar score), gestational duration, and diagnosis of small-for-gestational age, large for gestational age or intrauterine growth restriction. Data for the pregnant woman will include body weight development, hemoglobin, ferritin, plasma glucose, blood pressure delivery mode and

pregnancy complications (e.g. gestational diabetes, gestational hypertension, and preeclampsia). Analyses of genetic variants relating to D vitamin metabolism will also be analysed.

Analyses of serum 25OHD (25OHD3 and 25OHD2) and vitamin D metabolites (e.g. 3-epi-25-Hydroxyvitamin D3, 1,25-dihydroxyvitamin D [1,25(OH)2D]) and vitamin D binding proteins) in maternal blood will be performed by the golden standard method liquid chromatography tandem-mass spectrometry (LC-MS/MS) in a lab accredited by the vitamin D external quality assessment scheme (DEQAS; http://www.deqas.org). Analyses of serum from pregnant women will be performed in batch after the last sample collection. Other analyses of blood includes biomarkers of nutrition status (e.g. nutrients, ferritin, hemoglobin, and metabolomics), inflammation (e.g. CRP, interleukines and cytokines) and bone metabolism, hormones (e.g. cortisol, PTH and sex hormones), as well as gene variants related to vitamin D metabolism.

A total amount of 15 mL blood will be drawn at both screening and follow up. Thus, the total amount of blood drawn will be 30 mL.

Statistical analyses

Mixed models analyses will be used to investigate the change of vitamin D status over time, adjusting for potential confounders. Also, logistic regression will be performed to investigate the odds of ≥50 nmol/l and <50 nmol/l at follow-up. Interactions for BMI, ethnicity and season will be investigated. First the results including all completers will be evaluated (main analysis), thereafter intention-to-treat analysis will be performed including all randomized participants, and lastly per-protocol analysis will be performed including those >80% compliant. Differences in dropouts, compliance and missed visits will be compared between the three arms in order to detect potential bias. Logistic regression analysis will be used to assess differences in dichotomous outcomes (such as gestational complications) between treatment arms, and linear regression analysis for continuous outcome data. The study will be registered at https://clinicaltrials.gov.

TIME PLAN

Hanna Augustin has received funding for the study including from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-822451 and LFGBG-932690). Ethical approvals was obtained autumn 2021 (Dnr 2021-03871). Recruitment for the PREDIN RCT will start in winter 2021 and is projected to end by winter 2024. Thereafter, analysis of blood samples will be performed, followed by data handling, statistical analyses and reporting.

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