Original Investigation

Vitamin D Status During Pregnancy and Risk of Multiple Sclerosis in Offspring of Women in the Finnish Maternity Cohort

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IMPORTANCE Vitamin D has been associated with a decreased risk of multiple sclerosis (MS) in adulthood; however, some, but not all, previous studies have suggested that in utero vitamin D exposure may be a risk factor for MS later in life.

OBJECTIVE To examine whether serum 25-hydroxyvitamin D (25[OH]D) levels in early pregnancy are associated with risk of MS in offspring.

DESIGN, SETTING, AND PARTICIPANTS Prospective, nested case-control study in the Finnish Maternity Cohort conducted in May 2011. We identified 193 individuals with a diagnosis of MS before December 31, 2009, whose mothers are in the Finnish Maternity Cohort and had an available serum sample from the pregnancy with the affected child. We matched 176 cases with 326 controls on region of birth in Finland, date of maternal serum sample collection, date of mother's birth, and date of child's birth.

MAIN OUTCOMES AND MEASURES Maternal serum 25(OH)D levels were measured using a chemiluminescence assay. The risk of MS among offspring and association with maternal 25(OH)D levels were the main outcomes. Conditional logistic regression was used and further adjusted for sex of the child, gestational age at the time of sample collection, and season of sample collection to estimate the relative risks and 95% CIs.

RESULTS Of the 193 cases in the study, 163 were female. Of the 331 controls in the study, 218 were female. Seventy percent of serum samples were collected during the first trimester of pregnancy. The mean (SD) maternal vitamin D levels were in the insufficient vitamin D range, but higher in maternal control than case samples (15.02 [6.41] ng/mL vs 13.86 [5.49] ng/mL [to convert to nanomoles per liter, multiply by 2.496]). Maternal vitamin D deficiency (25[OH]D levels <12.02 ng/mL) during early pregnancy was associated with a nearly 2-fold increased risk of MS in the offspring (relative risk, 1.90; 95% CI, 1.20-3.01; $P = .006$) compared with women who did not have deficient 25(OH)D levels. There was no statistically significant association between the risk of MS and increasing serum 25(OH)D levels ($P = .12$).

CONCLUSIONS AND RELEVANCE Insufficient maternal 25(OH)D during pregnancy may increase the risk of MS in offspring.

Editorial

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Inadequate vitamin D nutrition has been identified as a risk factor for developing multiple sclerosis (MS),[1] a progressive, neurodegenerative disease of the central nervous system. Two previous prospective studies have found that elevated serum levels of 25-hydroxyvitamin D (25[OH]D), a marker of vitamin D nutrition, in healthy adults are associated with a decreased risk of MS,[2,3] and another prospective study among adult women[4] found that higher dietary intake of vitamin D was associated with lower MS risk. Whether this inverse association extends to vitamin D exposure in early life is not clear. Two Swedish prospective studies, one measuring maternal 25(OH)D levels during pregnancy[3] and the other measuring 25(OH)D levels in dried blood spots collected from newborns,[5] found no association with future MS risk in the child, while a study of gestational dietary vitamin D intake in US women found that higher intake was associated with a decreased risk of MS in the child.[6] Additionally, the higher number of spring births observed among patients with MS[7,8] has been attributed to exposure to lower vitamin D in utero, although other immune effects of sun exposure, seasonal infections, or statistical artifact[1,9] cannot be ruled out. Thus, whether adequate maternal vitamin D levels during pregnancy are associated with risk of MS in the offspring remains unclear.

We conducted a case-control study nested in the Finnish Maternity Cohort (FMC) to examine whether maternal levels of 25(OH)D during early pregnancy are associated with the risk of MS in the offspring.

Key Points

Question: Is maternal vitamin D deficiency during pregnancy associated with the risk of multiple sclerosis in the offspring?

Findings: In this prospective, nested case-control study within the Finnish Maternity Cohort, multiple sclerosis risk was 90% higher in offspring of vitamin D–deficient mothers (25-hydroxyvitamin D <12.02 ng/mL) compared with offspring of mothers who were not vitamin D deficient, a statistically significant difference.

Meaning: This result supports a role of prenatal vitamin D in determining multiple sclerosis risk and suggests that correction of vitamin D deficiency during pregnancy may reduce the risk of MS in the offspring.

Methods

Study Population

The FMC was established in 1983 and is composed of more than 800 000 women and more than 1.5 million serum samples[10] that were collected during their pregnancies at approximately 10 to 14 weeks' gestation for routine prenatal tests. The samples were collected at municipal maternity care units and shipped to the Finnish National Institute for Health and Welfare in Oulu, Finland, where they were processed and stored at −25°C.[11] The FMC includes samples from approximately 98% of all pregnancies in Finland since 1983. This study was approved by the data protection authorities at the National Institute for Health and Welfare, the Regional Ethics Committee of the Northern Ostrobothnia Hospital District, and the Office of Human Research Administration at the Harvard T. H. Chan School of Public Health. Since 2002, informed written consent has been obtained from the mothers to store the samples for research purposes; use of samples collected prior to 2002 for research purposes is allowed under Finnish law.

MS Case Identification and Control Selection

We identified cases of MS occurring among children born to women in the FMC between January 1, 1983, and December 31, 1991 (children who would be 18-27 years old by December 31, 2009), by searching the Finnish Hospital Discharge Register for the diagnostic codes for MS and related diseases (*International Statistical Classification of Diseases, Tenth Revision* codes G35, G36, and H46, and *International Statistical Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases, Eighth Revision* codes 340, 341, 367, and 377). This search was conducted in May 2011. The Finnish Hospital Discharge Register includes both inpatient and outpatient neurological visits. We also searched the registry of the Social Insurance Institution to identify cases not in the Finnish Hospital Discharge Register. The Social Insurance Institution tracks medication reimbursement for disease-modifying therapy and other treatments for MS, including glatiramer acetate, interferon β-1a, and interferon β-1b. Medical records of the children with MS were reviewed when available and the diagnosis confirmed by the study neurologists (M.S.-H., J.Å., K.H.). For cases that were identified through the Social Insurance Institution, an abstract of the medical record was obtained.

To identify the mothers of the individuals confirmed as having MS, an overgeneration linkage step was done via the Population Census Register. The mothers were then linked by their personal identification number to the FMC database and the pregnancy with the affected child was identified. The child/mother pair was included if there was a serum sample available from this pregnancy.

Multiple sclerosis was confirmed, and a maternal pregnancy serum sample was available for 193 children (138 cases of MS were confirmed by review of the medical record and 55 based on prescription of/reimbursement for MS disease-modifying therapy). We were able to individually match 176 of these cases to 326 controls on region of birth in Finland (south, southwest, southeast, middle, and north); date of maternal sample collection (±60 days); date of mother's birth (±6 months); and date of child's birth (±2 months). There were 17 cases for whom an appropriate matched control could not be found and an additional 5 controls that were selected, but ultimately not matched.

Serum 25(OH)D Measurement

Maternal 25(OH)D levels were measured in the prenatal serum sample taken from the mother during her pregnancy with the affected child or matched control child using a chemiluminescence microparticle immunoassay and an Architect i2000SR automatic analyzer (Abbott Diagnostics). Maternal 25(OH)D levels exhibited the expected seasonal variation: summer, 17.67 ng/mL (to convert to nanomoles per liter, multiply

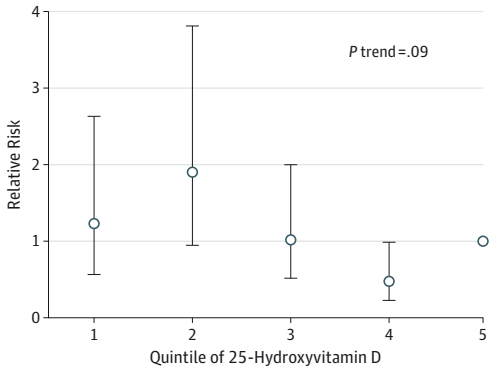
Table. Characteristics of Cases With MS and Controls, Finnish Maternity Cohort Offspring

Characteristic	Cases With MS (n = 193)	Controls (n = 331)
Female, No. (%)	163 (84)	218 (66)
Mother's age, mean (SD), y[a]	27.6 (5.3)	27.7 (5.4)
Gestational age, mean (SD), wk[a]	11.6 (3.9)	10.9 (3.3)
Season, No. (%)[a]		
Summer	74 (38.3)	140 (42.3)
Winter	52 (26.9)	85 (25.7)
Mother's 25(OH)D level, mean (SD), ng/mL	13.86 (5.49)	15.02 (6.41)
Age at MS diagnosis, mean (SD), y	19.8 (3.2)	NA

Abbreviations: MS, multiple sclerosis; NA, not applicable; 25(OH)D, 25-hydroxyvitamin D.

[a] At time of serum sample collection.

Figure 1. Multivariate Relative Risk for Multiple Sclerosis in Offspring by Quintiles of Maternal 25-Hydroxyvitamin D Level During Pregnancy



Median 25-Hydroxyvitamin D					
ng/mL	8.49	11.02	13.90	17.59	22.52
Range	3.49-9.50	9.62-12.50	12.62-15.50	15.58-19.51	19.71-64.50
Case/control No.	36/65	57/66	37/65	18/65	28/65

Adjusted for sex, gestational age, and season at time of sample collection. Error bars indicated 95% CIs.

by 2.496); winter, 11.58 ng/mL; and spring/fall, 13.22 ng/mL, with the latter seasons being statistically significantly lower than summer levels ($P < .001$ for both). Coefficients of variation derived from repeated quality-control samples included in the assay with the study samples were calculated. In samples with high 25(OH)D levels (> 40.06 ng/mL), the coefficient of variation was 3.5%; medium 25(OH)D levels (approximately 32.05 ng/mL), 1.8%; and low 25(OH)D levels (<16.03 ng/mL), 3.0%. In blinded quality-control pairs where 25(OH)D levels were not known, the coefficient of variation was 1.1%.

Statistical Analysis

The 25(OH)D levels were modeled in 3 ways: (1) as a continuous variable, (2) as quintiles based on the distribution of maternal 25(OH)D levels in the controls, and (3) as a priori categories consistent with deficient (<12.02ng/mL), insufficient (12.02 to <20.03ng/mL), and sufficient (≥20.03 ng/mL) levels per the Institute of Medicine's guidelines.[12] To account for the matched, nested, case-control design of the study, conditional logistic regression was used in the main analysis to estimate the rate ratios and 95% CIs and included the 176 cases with 326 matched controls. In addition to the matching factors, these analyses were further adjusted for sex of the child, gestational age (in days, continuous) at sample collection, and season (summer, winter, or spring/fall) of sample collection. In secondary analyses, we also performed an unconditional logistic regression adjusting for all the matching factors in addition to those listed previously in all 193 cases and 331 controls and stratified by sex of the child (female: 163 cases and 218 controls; male: 30 cases and 113 controls). A P value less than .05 was considered statistically significant, and all analyses were done using SAS, version 9.3 (SAS Institute Inc).

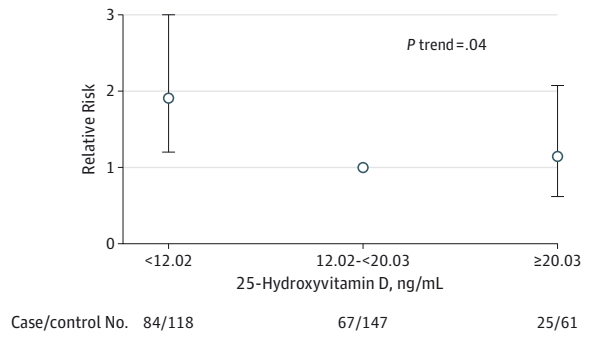
Results

Cases with MS and controls were similar with regard to mother's age, gestational age, and season at the time of serum sample collection (**Table**). The young average age at MS diagnosis reflects the fact that the source population comprises only individuals born after 1983. Seventy percent of serum samples were collected at or before 12 weeks' gestation and 99% prior to 28 weeks. There were more women in the case group and the mean (SD) age at MS diagnosis was 19.8 (3.2) years (Table). Maternal 25(OH)D levels ranged from 3.50 ng/mL to 64.30 ng/mL, with the average levels in the insufficient range of 25(OH)D and slightly lower in case mothers than in mothers of controls (Table). Only 2 cases with MS and 8 controls had maternal 25(OH)D levels of more than 30.05 ng/mL, and no MS cases and only 1 control had maternal 25(OH)D levels of more than 40.06 ng/mL. Mean 25(OH)D levels did not differ by trimester of serum collection (first trimester, 14.66 ng/mL and second trimester, 14.50 ng/mL). No cases and 2 controls had a mother with an MS diagnosis.

In the matched analysis adjusted for sex, gestational age, and season at time of sample collection, a 20.03-ng/mL increase in maternal 25(OH)D level was associated with a nonstatistically significant 48% reduced risk of MS in the offspring (relative risk [RR], 0.52; 95% CI, 0.22-1.19; $P = .12$). Children of mothers with deficient levels of 25(OH)D during their pregnancy had an increased risk of developing MS compared with children born to mothers with nondeficient levels. Specifically, maternal 25(OH)D levels of less than 12.62 ng/mL (quintiles 1 and 2) were associated with a 20% to 90% increased risk of MS among the offspring compared with maternal 25(OH)D levels in the top quintile (median 25[OH]D, 22.52 ng/mL; P trend = .09) (**Figure 1**). Similarly, in multivariate analyses using a priori categories of 25(OH)D levels, clearly deficient maternal 25(OH)D levels during pregnancy were associated with a nearly 2-fold increased risk of MS in the child (<12.02 ng/mL vs 12.02 to <20.03 ng/mL: RR, 1.90; 95% CI, 1.20-3.01; $P = .04$) (**Figure 2**).

Similar, although slightly attenuated, results were obtained in the unmatched analysis, with a 43% reduced risk of MS associated with every 4.01-ng/mL increase in maternal 25

Figure 2. Multivariate Relative Risk for Multiple Sclerosis in Offspring by Maternal 25-Hydroxyvitamin D Level Adequacy During Pregnancy



Adjusted for sex, gestational age, and season at time of sample collection. P = .006 for the relative risk in the <12.02 category vs the 12.02 to <20.03 category.

(OH)D level (RR, 0.57; 95% CI, 0.28-1.18; P = .13), and a 59% increased risk of MS among children born to mothers who were vitamin D deficient during pregnancy (<12.02 ng/mL vs 12.02 to <20.03 ng/mL: RR, 1.59, 95% CI, 1.04-2.42; P = .03). In analyses stratified by sex of the child, this association was only seen in female children (<12.02 ng/mL vs 12.02 to <20.03 ng/mL: RR, 1.75; 95% CI, 1.09-2.81; P = .02), although the sample size among male children was small.

Discussion

In this large, prospective, nested case-control study in the FMC, children of women who were vitamin D deficient (25[OH]D levels <12.02 ng/mL) early in their pregnancy had a 90% increased risk of developing MS as an adult. Two prior studies examining the association between 25(OH)D levels in pregnancy/early life did not find an association with future MS risk in the offspring.[3,5] However, there are important differences and limitations to these studies that need to be considered. In the Northern Sweden Maternity Cohort, Salzer et al[3] conducted a nested case-control study of primarily first trimester maternal 25(OH)D levels and risk of MS among the offspring; however, there were only 37 cases of MS among the offspring and the association between maternal 25(OH)D level and MS risk was fairly unstable, as evidenced by wide confidence intervals of the risk estimate (RR of MS in 25[OH]D ≥30.05 ng/mL vs <30.05 ng/mL, 1.8; 95% CI, 0.53-5.8), making interpretation, including conclusion of a true null association, difficult. In a 2014 Swedish case-control study, Ueda et al[5] measured 25(OH)D levels in dried blood spots collected for phenylketonuria screening from 459 cases with MS and 663 controls when they were newborns in 1975 or later. Overall, there was no association between neonatal 25(OH)D levels and risk of MS (odds ratio, 1.0; 95% CI, 0.90-1.06). However, there was evidence of 25(OH)D degradation in the older dried blood spot samples, which may have contributed to the null findings, although no associations were seen when restricting to more recent samples in which 25(OH)D degradation did not appear to occur. Another important concern is that with low overall control participation in the study (44% of those eligible), it is possible that the control participants did not provide an accurate representation of the 25(OH)D exposure distribution in the general population of newborns. Further, the levels of neonatal 25(OH)D in the Ueda et al[5] study were primarily in the deficient range (median, 10.26 ng/mL; interquartile range, 6.81-15.38 ng/mL) making it difficult to detect any association with 25(OH)D deficiency and MS risk.[13]

The strengths of our study included the population-based nature of the FMC (approximately 98% of pregnancies in Finland since 1983 are captured). Thus, selection bias is minimized, given the extensive national coverage of the Finnish Hospital Discharge Register and the Social Insurance Institution for MS case identification.

There are a few limitations of our study to consider. Maternal 25(OH)D levels during pregnancy are not a direct measure of the 25(OH)D levels that the developing fetus is exposed to. However, several studies have shown that the levels of serum 25(OH)D in neonates directly correlate with maternal 25(OH)D levels during pregnancy or postpartum,[14-16] with stronger correlations for the latter. Furthermore, studies of bone growth and development in the fetus[17,18] find that maternal vitamin D deficiency during pregnancy is associated with poorer bone health markers in the fetus. Collectively, these studies suggest that the maternal 25(OH)D levels are an adequate proxy for the 25(OH)D levels to which the fetus is exposed. Another consideration is that most of the samples from the FMC (>70%) were collected in the first trimester of pregnancy. Whether the association between maternal vitamin D deficiency and MS risk in the offspring is confined to the first trimester or whether similar associations would be seen with maternal vitamin D deficiency during the second or third trimesters cannot be directly assessed in our study, but it seems unlikely that many deficient women became sufficient later in pregnancy because even 25(OH)D levels collected during summer months were on average in the insufficient range (17.63 ng/mL). The average age at MS diagnosis was 19.8 years and the oldest age at diagnosis was 27 years. Thus, we cannot rule out the possibility that the association between maternal 25(OH)D levels during pregnancy and MS incidence decreases at older ages. We also did not have information on other MS risk factors the offspring may have had, such as Epstein-Barr virus infection, high body mass index in childhood/adolescence, cigarette smoking, vitamin D status, or human leukocyte antigen DRB1*1501 status, and cannot rule out confounding by these factors. Finally, the increased MS risk among individuals born to vitamin D-deficient mothers could be explained if these individuals had low circulating 25(OH)D levels during their childhood and early adult life. A positive correlation between maternal vitamin D status and the vitamin D status in her children would be expected because of probable similarities in behavior (eg, use of vitamin D supplements or sun protection) and shared genes. Although it has been demonstrated in a mendelian randomization study[19] that individuals carrying alleles associated with lower 25(OH)D levels have an increased MS risk, a result that supports a causal role of vitamin D in MS, the genetic contribution in our study is likely to be small because

genetically determined variations in 25(OH)D level are modest and only 50% of the maternal alleles are transmitted to the offspring. On the other hand, behavioral factors are more difficult to quantify, and we cannot estimate to what extent the effects of in utero exposure to vitamin D deficiency could be mediated by 25(OH)D levels later in life.

While the range of maternal 25(OH)D spanned levels of deficient to sufficiency, most women in our study had deficient or insufficient levels (<20.03 ng/mL), and only 10 mothers had levels above 30.05 ng/mL, 1 of whom had 25(OH)D levels above 40.06 ng/mL. Thus, while our results suggest that vitamin D deficiency during pregnancy increases MS risk in the offspring, our study does not provide any information as to whether there is a dose-response effect with increasing levels of 25(OH)D sufficiency. Similar studies in populations with a wider distribution of 25(OH)D are needed.

Conclusions

Correcting maternal vitamin D deficiency in early pregnancy may have a beneficial effect on risk of MS in the offspring.

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Study concept and design: Munger, Soilu-Hänninen, Surcel, Ascherio.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Munger.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Munger, Ascherio.
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Administrative, technical, or material support: Munger, Åivo, Hongell, Soilu-Hänninen.
Study supervision: Soilu-Hänninen, Ascherio.

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