Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort

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ABSTRACT

Background: Miscarriage is the most common negative outcome of pregnancy, and identification of modifiable risk factors is potentially of great importance for public health. Low vitamin D concentrations in pregnancy are widespread worldwide, and vitamin D deficiency is implicated in immune cell regulation at the feto-maternal interface and several diseases of pregnancy.

Objective: We investigated whether 25-hydroxyvitamin D serum concentration was a modifiable risk factor for early miscarriage.

Design: In a prospective cohort study of 1683 pregnant women donating serum before gestational week 22, we investigated the association between maternal serum concentrations of 25-hydroxyvitamin D (25(OH)D) and the risk of subsequent miscarriage (n = 58).

Results: The adjusted hazard of first-trimester miscarriage was lower with higher 25(OH)D concentrations (HR: 0.98; 95% CI: 0.96, 0.99). Concentrations of 25(OH)D <50 nmol/L were associated with a >2-fold increased adjusted HR for miscarriage (HR: 2.50; 95% CI: 1.10, 5.69). Concentrations of 25(OH)D were not associated with an increased risk of second-trimester miscarriage.

Conclusions: We found an association between 25(OH)D and first-trimester miscarriages, suggesting vitamin D as a modifiable risk factor for miscarriage. To test this hypothesis, randomized controlled trials should investigate the possible effect of vitamin D supplementation to increase 25(OH)D concentrations in early pregnancy, or before conception, to decrease risk of miscarriage. This trial was registered at clinicaltrials.gov as NCT02434900.

INTRODUCTION

Miscarriage is the most common adverse outcome of pregnancy, with a reported prevalence of 12–20% (1). Miscarriage is multifactorial of origin, with acquired or environmental factors probably exceeding genetic factors in its causation (2–5). Identifying modifiable risk factors for miscarriage is potentially important for public health. A recent Danish study found that increased maternal age, alcohol consumption, prepregnancy BMI, heavy lifting, and nightshift work were important, preventable risk factors of miscarriage (6).

The human fetus represents a semi-allograft, which cannot survive without maternal immune tolerance (7, 8). Vitamin D may be implicated in the risk of miscarriage due to its function as an immune modulator (9, 10) and its potential importance for the maternal-fetal immunologic response (11). Vitamin D concentrations in serum are best assessed by the precursor hormone, 25-hydroxyvitamin D (25(OH)D) concentration. There is conflicting evidence with respect to 25(OH)D concentrations in pregnancy and associations to adverse pregnancy outcomes. With respect to preeclampsia, a number of studies have shown an increased risk of 25(OH)D concentrations <50 nmol/L, whereas some studies failed to find a significant correlation between 25(OH)D concentrations and the risk of preeclampsia. However, a recent meta-analysis of cohort studies showed a pooled crude OR (95% CI) of 2.09 (1.50, 2.90) for preeclampsia if 25(OH)D concentrations in pregnancy were <50 nmol/L (12). With respect to risk of small-for-gestational-age infants, the literature is also conflicting; however, in a meta-analysis from the same review, the pooled crude OR (95% CI) was 1.52 (1.08, 2.15) for small-for-gestational-age infants if 25(OH)D concentrations in pregnancy were <50 nmol/L.

1 Supported by The Region of Southern Denmark; Hans Christian Andersen’s Children’s Hospital and Odense University Hospital; The Municipality of Odense; A. J. Andersen’s Foundation, Denmark; and The Foundation for Promotion of Medical Science, A. P. Møller’s Foundation, Denmark. The Municipality of Odense and Odense University Hospital provided core funding support for the Odense Child Cohort study. Other contributors were the Mental Health Service in the Region of Southern Denmark, K. A. Rohde’s and wife’s Foundation, the Ronald McDonald Child Foundation, the Health Insurance Foundation, and the Odense University Hospital Research Fund.

2 Supplemental Material and Supplemental Table 1 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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The human placenta is a major extrarenal site for conversion of 25-hydroxyvitamin D$_3$ [25(OH)-D$_3$] to active 1,25-dihydroxycholecalciferol [1,25(OH)$_2$-D$_3$] (13). The converting enzyme, CYP27B1, and the vitamin D receptor are abundantly expressed in decidua and placenta in the first and second trimesters but subsequently decrease in the third trimester (14). Animal studies have demonstrated that administration of active 1,25(OH)D promotes endometrial decidualization (15), and 1,25(OH)D stimulates production of estradiol, progesterone, and human chorionadotropin in human trophoblast (16, 17).

1,25(OH)$_2$-D$_3$ is thought to have potent anti-inflammatory effects at the materno-fetal interface, promoting Th2 response (18) and differentiation of regulatory T cells (19) while down-regulating Th17-producing cells (20). In early pregnancy, vitamin D receptor and CYP27B1 expression was increased when subjected to increased concentrations of inflammatory cytokines (21), and direct application of 1,25(OH)$_2$-D$_3$ to stromal cells in vitro affected the production and profile of cytokines (22). 1,25(OH)$_2$-D$_3$ can also regulate HOXA10, which is necessary for embryo implantation and fertility (23). Thus, it is plausible that higher vitamin D concentrations in early pregnancy promote successful embryonic and fetoplacental development.

We used prospective data from the Odense Child Cohort to examine the hypothesis that low concentrations of maternal serum 25(OH)D during the first trimester increase the risk of early miscarriage.

**METHODS**

The Odense Child Cohort study is a population-based cohort study comprising pregnant women recruited between 1 January 2010 and 31 December 2012 (24). All women who were pregnant in the municipality of Odense during this time were eligible for participation, and 6707 women were approached directly with recruitment material.

From a population base of 6707 pregnant women, 2,874 (42.9%) enrolled in the Odense Child Cohort study up to 31 December 2012 (Figure 1). Of the participants, 1684 (58.6%) provided a blood sample before gestational age 22 + 0 wk calculated from first-trimester ultrasound data if available or date of last menstrual period. Samples were identifiable for the researchers and linked to data collected in the cohort. Miscarriage was defined as a missed miscarriage, a complete or incomplete miscarriage, or a blighted ovum before 22 completed weeks of gestation. The gestational date of miscarriage was defined as the date of diagnosis by transvaginal ultrasound. A miscarriage was also defined as spontaneous if fetal death and/or signs and symptoms of miscarriage had begun but not completed (i.e., rupture of membranes or regular contractions before 20 completed weeks of gestation).

The date of the last menstrual period, pregestational BMI, maternal age, smoking habits, and parity were extracted from self-reported data at the first antenatal visit, which took place before the miscarriage occurred, reducing the risk of recall bias. Smoking was defined as smoking during early pregnancy in any quantity. Maternal age at the time of delivery was recorded. The season of blood sampling was defined as either May to October or November to April, representing the seasons of high and low 25(OH)D concentrations, respectively (25). All these covariates—BMI, age, smoking habits, parity, and season of blood sampling—have been demonstrated to influence 25(OH)D concentrations (25). The study complied with the Helsinki Declaration and was approved by the Regional Scientific Ethical Committee for Southern Denmark, no. S-20090130. All participants gave informed consent.

**Biochemical analyses**

Measurement of 25(OH)D has been described in detail previously (25). 25(OH)D is a fat-soluble steroid hormone, with a half-life of ~2 wk. In short, the concentration of serum 25(OH)D was measured by liquid chromatography–mass spectrometry on a Thermo Scientific TLX1 system connected to a Thermo Scientific Vantage TSQ. The concentration relied on the determination of both 25-hydroxyvitamin D$_2$ [25(OH)-D$_2$] and 25(OH)-D$_3$ (25). The C3 epimer of vitamin D$_3$ was detected along with vitamin D$_3$, and both were not distinguishable from one another. Lowest detectable concentrations were 0.15 nmol/L for both vitamins D$_2$ and D$_3$. Values of vitamins D$_2$ and D$_3$ were only considered if >6.5 nmol/L. The method was externally calibrated against National Institute of Standards and Technology, Standard Reference Material 972 (26).

**Statistical analyses**

Variables were reported as means ± SDs or as medians (25th–75th percentiles) according to data distribution. Crude comparisons between miscarriage and nonmiscarriage groups were done with the Student’s t test or Mann-Whitney test as appropriate. To take into account left truncation, we constructed a Cox proportional hazards regression model to analyze the effect of 25(OH)D concentrations relative to the risk of miscarriage. A pregnancy was considered to be at risk of miscarriage from enrollment in the study until 1) miscarriage occurred, 2) provoked...
abortion on request, or 3) survival until 22 wk of gestation. Furthermore, stratified models according to first- or second-trimester miscarriage were performed. The regression analyses were performed by using 25(OH)D as a continuous variable and dichotomized by cutoff values of 50 nmol/L, and 75 nmol/L, respectively. Analyses were adjusted for BMI, parity, season of blood sampling, and age as covariates. Smoking was not included because only 1 smoker was in the miscarriage group. Furthermore, for conditional logistic regression analysis, women with first-trimester miscarriage were matched 1:1 on exact gestational age at blood sampling to women without miscarriage. In case multiple suitable controls were found, one was picked at random, blinded to 25(OH)D status. Analysis in this subgroup was further adjusted for BMI, parity, season of blood sampling, and age. For logistic regression analysis, a logistic regression model was constructed comparing women with first-trimester miscarriage to all women with no miscarriage, with gestational age at blood sampling, BMI, parity, season of blood sampling, and age as covariates. Analysis in this subgroup case multiple suitable controls were found, one was picked at random, blinded to 25(OH)D status. Analysis in this subgroup was further adjusted for BMI, parity, season of blood sampling, and age. For logistic regression analysis, a logistic regression model was constructed comparing women with first-trimester miscarriage to all women with no miscarriage, with gestational age at blood sampling, BMI, parity, season of blood sampling, and age as covariates. STATA 12.0 (StataCorp) was used for all data analysis. Significance level was set at $P < 0.05$ by using 2-sided tests.

RESULTS

Among the 2874 participating women in the Odense Child Cohort, 88 (3.1%) had a miscarriage. Of the 1684 women who had available information on 25(OH)D concentration before gestation 22 + 0 wk, 59 women (3.5%) had a miscarriage. Of these, 1 woman was diagnosed with miscarriage on the day of blood sampling and was excluded from the Cox regression (entering and leaving study on same date), resulting in a final study population of 1683 women, of whom 58 had a miscarriage (3.5%), 25 in the first trimester and 33 in the second trimester (Figure 1). Most women who had a miscarriage provided blood in the first trimester ($n = 56; 96.6%$); only 2 provided blood in the second trimester. Of the 1190 participants who did not provide a blood sample before 22 completed weeks of gestation, 29 (2.4%) had a miscarriage. In the group that provided a blood sample, the miscarriage occurred at a median gestational age of 87 d (IQR: 78–90 d), and in women who did not provide a blood sample, the miscarriage occurred at a median gestational age of 88.5 d.

In our study population, the miscarriage group had lower maternal serum concentrations of 25(OH)D at the time of sampling (miscarriage median 55.55 nmol/L vs. nonmiscarriage median 66 nmol/L; $P = 0.002$, Mann-Whitney rank-sum test), with blood samples taken earlier than in the nonmiscarriage group (gestational age 69 d vs. 84 d; $P < 0.0001$, Mann-Whitney rank-sum test) (Table 1). The miscarriage group did not differ from the background population in maternal age, BMI, or parity. Within the miscarriage group, those women who had a miscarriage in the first trimester of pregnancy had a tendency to have lower concentrations of 25(OH)D ($P = 0.053$) and earlier blood sampling compared with those women who had a miscarriage in the second trimester ($P = 0.08$).

25(OH)D concentrations tended to increase with gestational age at blood sampling, for both women who had miscarriages and the rest of the cohort (Figure 2).

Higher concentrations of 25(OH)D were associated with slightly lower HRs for miscarriage in overall adjusted analysis, although this did not reach statistical significance (Table 2). In adjusted Cox regression analyses stratified by first- or second-trimester miscarriage, the risk of first-trimester miscarriage was substantially lower with higher 25(OH)D concentrations (HR: 0.98; $P = 0.049$), and if concentrations were $< 50$ nmol/L, the HR for miscarriage was increased $\geq 2$-fold (HR: 2.5; $P = 0.028$). A trend was also seen toward a higher hazard for miscarriage with concentrations $< 75$ nmol/L (HR: 5.7; $P = 0.089$).

We performed a post hoc power calculation by using the estimates from the proportional hazards model with the Cox proportional hazards regression/Wald test. For 25(OH)D $< 50$ nmol/L as the exposure of interest for first-trimester miscarriage, current sample size with 25 events had a power of 0.30 and an unadjusted HR of 2.1 ($P = 0.06$). To achieve a power of 0.80 with a prevalence of 1.5% first-trimester miscarriages, a sample size of 6205 would be needed with 95 cases of first-trimester miscarriage to detect a true, unadjusted association. Because we detected an adjusted association with even lower case numbers, our study was not considered underpowered.

For miscarriages in the second trimester, there was no evidence of increased risk of miscarriage with low 25(OH)D concentrations (Table 2). Age, prepregnancy BMI, parity, and seasonal variation did not affect the risk of miscarriage in adjusted analyses (data not shown).

Women who miscarried had donated blood for 25(OH)D analysis earlier than did women with healthy pregnancies in the present study. Because gestational age at blood sampling was the entry point for Cox regression analysis, correction for this variable could not be performed by inclusion as a covariate. However, we performed a conditional logistic regression analysis with exact matching on gestational age at blood sampling (Table 3). In this analysis, women who had 25(OH)D concentrations $< 50$ nmol/L had an OR of 3.86 (95% CI: 1.02, 14.63) for first-trimester miscarriage ($n = 25$) compared with those with 25(OH)D $\geq 50$ nmol/L ($n = 25$). Furthermore, we performed ordinary logistic regression analysis with correction for gestational age at blood sampling in the whole cohort (Supplemental Material, Supplemental Table 1). In this analysis, women who had 25(OH)D concentrations $< 50$ nmol/L had an OR of 2.43 (95% CI: 1.02, 14.63) for first-trimester miscarriage ($n = 26$) compared with those with 25(OH)D $\geq 50$ nmol/L.

DISCUSSION

This prospective cohort study analyzed the association between 25(OH)D concentrations and the subsequent risk of miscarriage as the primary outcome. We demonstrate that low serum concentrations of 25(OH)D were associated with an increased risk of miscarriage in the first but not in the second trimester. The mean half-life of 25(OH)D is 2 wk (27), and exposure to certain chemicals or drugs in the first trimester increases the risk of miscarriage or severe malformations. We considered that the 25(OH)D concentration measured in our cohort with predominantly first-trimester blood sampling was most representative for women who had miscarriages before 12 wk of gestation.

To our knowledge, no randomized controlled trial has been performed with the objective of investigating the effect of 25(OH)D concentrations on the occurrence of miscarriage (28). However, some recent observational studies have looked at miscarriage as secondary outcomes. In a small Danish cohort study, 3 women with miscarriage between 10 and 22 wk of gestation had
lower 25(OH)D than 84 controls who completed their pregnancy (29). In addition, in a randomized controlled trial of different supplementary doses of 25(OH)D, women who had a pregnancy loss had a nonsignificant trend toward lower 25(OH)D concentrations at 12 wk of gestation compared with women who delivered a live infant [25(OH)D concentrations: 23.2 nmol/L vs. 23.6 nmol/L (95% CI: 21.8, 25.4) (30)]. Pregnancy loss included miscarriage as well as later fetal death up to 34 wk of gestation. In an Australian cohort, no significant difference was found between 25(OH)D concentrations in gestational weeks 10–14 in women who miscarried, with mean 25(OH)D concentrations of 56.9 nmol/L (95% CI: 54.9, 59.0) vs. 53.5 nmol/L (95% CI: 50.7, 56.2) (31). In a recent study of 133 women with 3 or more recurrent pregnancy losses, women with 25(OH)D <30 ng/mL (75 nmol/L) had increased risk of autoimmune and abnormal cellular immune responses (36). Similarly, in vitro studies involving endometrial cells from women with spontaneous recurrent miscarriage demonstrated that stimulation with 1,25(OH)2-D3 modulated the release of cytokines (22).

It has also been suggested that vitamin D is important for the success of in vitro fertilization (37) and the prevalence of bacterial vaginosis, which in turn has been associated with early, late, and recurrent miscarriage (38, 39).

Accordingly, it is compelling to hypothesize an active role for vitamin D at the feto-maternal immunologic interface and hence a role in miscarriage. Vitamin D insufficiency, defined as 25(OH)D concentrations in human placenta may have a direct impact on the cytokine profile and the inflammatory response (35).

### TABLE 1

**Characteristics of participants**

<table>
<thead>
<tr>
<th>Participants, n</th>
<th>No miscarriage</th>
<th>Miscarriage</th>
<th>P value</th>
<th>First-trimester miscarriage</th>
<th>P value</th>
<th>Second-trimester miscarriage</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D, nmol/L</td>
<td>66.0 (50.37–80)</td>
<td>55.6 (43.60–69.92)</td>
<td>0.002</td>
<td>50.81 (39.90–74.66)</td>
<td>0.002</td>
<td>57.0 (50.52–74.66)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood sampled in summer season, n (%)</td>
<td>809 (49.8)</td>
<td>28 (48.3)</td>
<td>NS</td>
<td>11 (45.8)</td>
<td>NS</td>
<td>17 (51.5)</td>
<td>NS</td>
</tr>
<tr>
<td>GA blood sampling, d</td>
<td>84 (72–104)</td>
<td>69 (64–76.53)</td>
<td>&lt;0.0001</td>
<td>64.5 (61–78)</td>
<td>&lt;0.0001</td>
<td>74 (69–78.04)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maternal prepregnancy BMI, kg/m²</td>
<td>23.38 (21.26–26.18)</td>
<td>23.26 (21.01–27.18)</td>
<td>NS</td>
<td>23.46 (22.49–27.41)</td>
<td>NS</td>
<td>23.22 (20.80–26.49)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking in pregnancy, n (%)</td>
<td>83 (5.1)</td>
<td>1 (1.7)</td>
<td>NS</td>
<td>1 (4.0)</td>
<td>NS</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Parity, n (%)</td>
<td>Nullipara 922 (56.7)</td>
<td>30 (51.7)</td>
<td>NS</td>
<td>14 (56)</td>
<td>NS</td>
<td>16 (48.5)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Primipara 543 (33.4)</td>
<td>22 (37.9)</td>
<td>NS</td>
<td>8 (32)</td>
<td>NS</td>
<td>14 (42.4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Secundipara 128 (7.9)</td>
<td>5 (8.6)</td>
<td>NS</td>
<td>3 (12)</td>
<td>NS</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tercipara or more 32 (2.0)</td>
<td>1 (1.7)</td>
<td>NS</td>
<td>1 (3.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistical test used: Student’s t test for parametric data, Mann-Whitney test for nonparametric data, and Fisher’s exact test for 2 × 2 tables. P values represent comparisons with the no-miscarriage group. GA, gestational age; 25(OH)D, 25-hydroxyvitamin D.*

**FIGURE 2** Scatterplot of serum 25(OH)D vs. gestational age at blood sampling. Light gray squares represent miscarriages (n = 58); dark gray circles represent the rest of the cohort. Solid trend line: miscarriages; dashed trend line: the rest of the cohort. 25(OH)D, 25-hydroxyvitamin D.
either <50 nmol/L or <75 nmol/L, is prevalent in pregnancy worldwide (11), suggesting that hypovitaminosis D may be an important preventable risk factor for miscarriage in the first trimester. Major strengths of this study include the prospective design, in which women did not know their vitamin D concentrations; the large sample size; and the ability to adjust for variables such as parity, BMI, and season of sampling. We had accurate knowledge of 25(OH)D concentrations, which can be considered representative of the value at the time of miscarriage. Although our cohort had high concentrations of 25(OH)D compared with other studies, and our cohort sample comprised fewer women of non-European ethnic origin than our background population (25), we were able to detect an association between low 25(OH)D and miscarriage, suggesting that the magnitude of the effect in a less homogeneous population may be even higher than detected.

The limitations of our study include the observational nature of a pregnancy cohort and the low number of miscarriages, as women were enrolled in the late first trimester after pregnancy was detected. The prevalence of miscarriages after the late first-trimester enrollment in our study is comparable to other studies [e.g., Hoesli et al. (40), who reported a 2.44% fetal loss rate in gestational weeks 8–14]. Given the low prevalence of vitamin D insufficiency, our study was marginally underpowered for an optimally designed study, higher numbers of samples and a preemptive power calculation should have taken the effect of increasing 25(OH)D concentrations by supplementation into account. Further limitations included a nonparticipation rate of 57.1% from women within the background population in the cohort and the collection of early pregnancy blood samples in only 58.6% of participants. However, women who did not provide blood samples had a lower frequency of miscarriages, suggesting that the women had a lower miscarriage risk.

With regard to residual confounding, we were unable to adjust the association between 25(OH)D and miscarriage for variables such as socioeconomic status, dietary habits, and use of prenatal vitamins and folic acid, because women who miscarried dropped out before completing the cohort questionnaires. Finally, our laboratory method for determining serum 25(OH)D was sound but lacked a subdetermination of the concentration of C3 epimer (41, 42).

In conclusion, we found an association between 25(OH)D concentrations and first-trimester miscarriage, indicating that vitamin D concentrations <50 nmol/L in the first trimester were associated with an HR of 2.5 for a subsequent first-trimester miscarriage. These findings suggest a protective role for vitamin D against miscarriage. To test this hypothesis, randomized controlled trials should be performed to investigate the possible effect of increasing 25(OH)D concentrations by supplementation in early pregnancy or even preconceptually.

The authors’ responsibilities were as follows—LBA, JSJ, TKJ, CD, TB, SH, and HTC: designed the research project; LBA, CD, and JN: performed the statistical analysis; LBA, JSJ, TKJ, TB, SSB-N, SH, RFL, BA, and HTC: wrote the manuscript; LBA: had primary responsibility for the manuscript’s final content; BA: contributed to manuscript writing and statistical analysis; and all authors: read and approved the final version of the manuscript. All authors declared no conflicts of interest or competing interests. No funders had any influence on the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

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**TABLE 2**

Crude and adjusted HRs for miscarriage

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage overall</th>
<th>First-trimester miscarriage</th>
<th>Second-trimester miscarriage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Crude HR (95% CI)</td>
</tr>
<tr>
<td>25(OH)D, nmol/L</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.98 (0.96, 1.00)</td>
</tr>
<tr>
<td>25(OH)D &lt;50 vs. ≥50</td>
<td>1.24 (0.73, 2.13)</td>
<td>1.28 (0.74, 2.26)</td>
<td>2.15 (0.98, 4.72)</td>
</tr>
<tr>
<td>25(OH)D &lt;75 vs. ≥75</td>
<td>1.60 (0.78, 3.27)</td>
<td>1.64 (0.80, 3.38)</td>
<td>5.48 (0.74, 40.62)</td>
</tr>
</tbody>
</table>

1Statistical test used: Cox proportional hazards regression model, adjusted for season of blood sampling, parity, maternal BMI, and maternal age.

**TABLE 3**

Conditional matched case-control analysis

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage overall, n = 57 vs. n = 57</th>
<th>First-trimester miscarriage, n = 25 vs. n = 25</th>
<th>Second-trimester miscarriage, n = 32 vs. n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td>Crude OR (95% CI)</td>
</tr>
<tr>
<td>25(OH)D, nmol/L</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.98 (0.94, 1.02)</td>
</tr>
<tr>
<td>25(OH)D &lt;50 vs. ≥50</td>
<td>1.24 (0.73, 2.13)</td>
<td>1.28 (0.74, 2.26)</td>
<td>2.92 (0.87, 9.78)</td>
</tr>
</tbody>
</table>

1Statistical analysis used: conditional matched logistic regression with exact matching on gestational age at blood sampling. Covariates in adjusted analysis: maternal age, maternal prepregnancy BMI, parity, and season of blood sampling. *P < 0.05. 25(OH)D, 25-hydroxyvitamin D.
REFERENCES