Maternal Level of 25-Hydroxyvitamin D during Pregnancy Associated with Risk of Type 1 Diabetes in the Offspring, a Meta-Analysis

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Summary This aim of this meta-analysis was to evaluate the association between risk of childhood type 1 diabetes and maternal 25-hydroxyvitamin D [25(OH)D] levels during pregnancy. A literature search on databases including PubMed and Embase was conducted up to December 2018. The pooled odds ratio weighted mean difference (WMD) and the corresponding 95% confidence intervals (CIs) were calculated using the RevMan 5.3 software. A total of 4 studies were included in this meta-analysis. The overall analysis indicated that the maternal 25(OH)D levels during pregnancy was significantly associated with the risk of type 1 diabetes in offspring (WMD = 2.54, 95% CI = -4.65 to -0.44, p = 0.02). The subgroup analyses showed that sample for detection vitamin D (serum/plasma) may not a factor influencing the results of this meta-analysis. However, gestational trimester may be a factor affecting the results. The results showed that no significant association was observed between risk of type 1 diabetes in offspring and 25(OH)D level during first or second gestational trimester (p > 0.05). Lower maternal 25(OH)D levels during pregnancy is associated with higher risk of type 1 diabetes in offspring. Gestational trimester may be a factor influencing the results of this meta-analysis.

Key Words maternal vitamin D level, childhood glycometabolism, gestational trimester, association exploration, factor analysis

Type 1 diabetes is characterized as diabetes caused by the immune system attacking and destroying the beta cells in the pancreas that produce insulin. It is commonly occurred in childhood and the incidence is still increasing in recent years (1). Some studies have reported the role of vitamin D in the prevention of diabetes (including type 1 and type 2 diabetes) (2–5). Moreover, many studies have found that vitamin D intake during early life may be associated with a reduced risk of type 1 diabetes (6).

Many studies have investigated the risk factors of type 1 diabetes from the mothers, such as maternal obesity (7, 8), maternal smoking during pregnancy (9), and maternal vitamin D intake (10). Thus, we inferred the maternal vitamin D may be one of the risk factors of type 1 diabetes. Currently, some studies have investigated the association between risk of childhood type 1 diabetes and maternal 25-hydroxyvitamin D [25(OH)D] levels during pregnancy (11). For example, the studies performed by Sørensen et al. indicated that the lower serum concentration of vitamin D during pregnancy was associated with the higher risk of type 1 diabetes in children (12, 13). However, Miettinen et al. found the 25(OH)D concentration during early pregnancy are not associated with higher risk of type 1 diabetes (14, 15). Thus, there is controversies among previous studies.

For comprehensively evaluating the role of maternal 25(OH)D levels during pregnancy in risk of type 1 diabetes in the offspring, it is necessary to performed this meta-analysis.

MATERIALS AND METHODS

The methods used for this meta-analysis and generation of inclusion criteria were based on PRISMA recommendations.

Literature search strategy. Databases including PubMed and Embase were used for literature search up to December 2018, using the following search strategy: “type 1 diabetes” AND “Vitamin D” AND “Maternal” or “pregnancy.” For accurate retrieval, the search fields only included “Abstract” and “Title.” In case of omissions, the references of relevant reviews were also searched.

Inclusion and exclusion criteria. The inclusion criteria were as follows: (1) study type was case-control study; (2) cases were women whose offspring suffers from type 1 diabetes and controls were women whose offspring does not suffer from type 1 diabetes; (3) the level of 25(OH)D during pregnancy were reported; (4) only articles with full-text access were included.

The exclusion criteria were (1) duplicated publications or (2) reviews, letters, or comments.

Data extraction. The following data were recorded in a predesigned form: first author name, country, publication year, sample size, age of child at diagnosis of type 1
diabetes, age of mother at delivery, sex of child, sample for detecting 25(OH)D, gestational trimester and outcome. Data extraction was independently performed by two investigators. Differences were resolved by discussion to ensure consistent evaluation.

The study quality of these studies was evaluated by the Newcastle-Ottawa Scale (NOS). We assigned scores of 0–3, 4–6, and 7–9 for low, moderate, and high quality of studies, respectively.

**Statistical analysis.** The RevMan 5.3 and Stata 11.0 software was used for this meta-analysis. The I^2 and Cochran Q tests were used to assess heterogeneity among the included studies, with p values of <0.1 or I^2 values of >50% being considered as significant. An appropriate model (fixed- or random-effects model) was used to pool weighted mean difference (WMD) and the corresponding 95% confidence intervals (CIs) based on the results of the heterogeneity test. The publications bias was evaluated by Egger’s or Begg’s test. When significant publication bias was found, trim and fill method was used to evaluate the stability of the results. The subgroup analyses were performed by sample sources for detecting 25(OH)D and gestational trimester. For these analyses, p values of <0.05 indicated statistical significance.

**RESULTS**

**Characteristics of the included studies**

After an initial literature search, 261 articles were identified. By excluding duplicates and obvious irrelevant studies, 40 potentially relevant articles were remained. Of these, 36 studies were excluded, including 24 studies which did not report the level of maternal 25(OH)D during pregnancy, 3 studies which did not report the type 1 diabetes during offspring, 6 reviews and 3 duplicates. Finally, 4 studies (12, 13, 15, 16) were included in this meta-analysis (Fig. 1).

The publication year of these included studies ranged from 2012 to 2017. Three studies were conducted in Norway and one study was conducted in Finland. The serum/plasma level of maternal 25(OH)D during pregnancy was detected in these studies. The blood samples were from mothers during first/second/third gestational trimester. Based on the NOS scores, all these studies were moderate-quality studies (Table 1).

**Meta-analysis**

As shown in Fig. 2, significant heterogeneity among studies (p=0.04 or I^2=52%) were found, so the random effects model was used for pooling data. The pooled estimate indicated that the maternal 25(OH)D levels during pregnancy was significantly associated with the risk of type 1 diabetes in offspring (WMD=−2.54, 95% CI=−4.65 to −0.44, p=0.02, Fig. 2A). Lower maternal 25(OH)D levels during pregnancy can significantly increase the risk of type 1 diabetes in offspring. The subgroup analyses were performed by sample sources for detecting 25(OH)D or gestational trimester, as shown in Fig. 1. After excluding the one study in which plasma was used to detect the level of 25(OH)D (16), no inconsistent result was found (WMD=−3.95, 95% CI=−7.56 to −0.33, p=0.03, Fig. 2B).

However, the results showed that the maternal 25(OH)D level during first gestational trimester is not significantly associated with higher risk of type 1 diabetes in offspring when we performed this meta-analysis using the data of first gestational trimester (plasma and serum samples: WMD=−2.02, 95% CI=−4.91 to 0.88, p=0.17, Fig. 3A; only serum samples: WMD=−1.50, 95% CI=−5.86 to 2.86, p=0.50, Fig. 3B). Moreover, the meta-analysis using data of second gestational trimester (serum and plasma samples, WMD=−0.65, 95% CI=−3.13 to 1.83, p=0.61, Fig. 4A; only plasma samples, WMD=−0.10, 95% CI=−2.87 to 2.68, p=0.94, Fig. 4B) also showed no significant association between risk of type 1 diabetes in offspring and level of 25(OH)D level during second gestational trimester.
Table 1. Characteristics of included studies.

| Author     | Year | Country  | Group | Sample size | Age of child at diagnosis of type 1 diabetes | Mother’s age at delivery | Sex of child F/M | Gestational trimester | Level of VtD (Mean ±SD) | Sample for detection | NOS |
|------------|------|----------|-------|-------------|---------------------------------------------|--------------------------|------------------|----------------------|------------------------|----------------------|-----|
| Sørensen 2012 Norway Case | 109  | Mean =9.0 SD = 3.6 | Mean =28.2 SD = 5.7 | 63/46 | Median IQR 37 (22–38) wk | 65.8±26.5 | Serum | 6 |
| Control | 219  | NA       | Mean =28.3 SD = 5.2 | 98/121 | Median IQR 37 (24–38) wk | 73.1±27.2 |
| Miettinen 2012 Finland Case | 343  | Mean =3.4 Range=(0–7) | NR | NR | First trimester | 43.9±16.9 | Serum | 6 |
| Control | 343  | NA       | NR | NR | First trimester | 43.5±16.6 |
| Sørensen 2016 Norway Case | 113  | Mean =9.0 SD = 3.5 | Mean =28.2 SD = 5.6 | 65/48 | First trimester Second trimester Third trimester | 57.9±18.8 | Serum | 6 |
| Control | 220  | NA       | Mean =28.3 SD = 5.3 | 98/122 | First trimester Second trimester Third trimester | 62±19.1 | 68.4±24.4 | 75±27.9 |
| Thorsen 2017 Norway Case (DNBC) | 270  | Median=9.0 IQR=(5.7–11.1) | Median=30 IQR=(26.8–32.6) | 138/132 | First trimester Second trimester | 51.56±23.18 | Plasma | 6 |
| Control | 985  | NA       | Median=30 IQR=(27–33) | 497/488 | First trimester Second trimester | 54.8±21.23 | 60.8±20.32 |
| Case (MoBa) | 189  | Median=5.7 IQR=(3.6–7.9) | Median=30 IQR=(27–33) | 93/96 | Second trimester | 58.5±26.74 |
| Control | 576  | NA       | Median=30 IQR=(27–33) | 285/291 | Second trimester | 58.3±24 |

SD: standard deviation; IQR: interquartile range; NOS: Newcastle-Ottawa Scale; NA: not applicable; NR: not reported.
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Fig. 2. Forest plots for overall meta-analysis of association between risk of childhood type 1 diabetes and maternal 25-hydroxyvitamin D levels during pregnancy (A: serum and plasma samples; B: only serum samples).

#### A

| Study or Subgroup | Case | Control | Mean Difference | Mean Difference |
|-------------------|------|---------|-----------------|-----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Ingvid M. Sorensen 2012 | 65.8 | 26.5 | 109 | 73.1 | 27.2 | 219 | 8.1% | -7.30 [-13.44, -1.16] | |
| Ingvid M. Sorensen 2016-First trimester | 57.9 | 18.8 | 113 | 62 | 19.1 | 220 | 12.5% | -4.10 [-8.39, 0.19] | |
| Ingvid M. Sorensen 2016-Second trimester | 65.6 | 24.2 | 113 | 68.4 | 24.4 | 220 | 9.3% | -2.80 [-8.30, 2.70] | |
| Ingvid M. Sorensen 2016-Third trimester | 65.9 | 28.5 | 113 | 75 | 27.9 | 220 | 7.6% | -6.10 [-15.52, 2.68] | |
| Mattinen 2012 | 43.9 | 16.9 | 343 | 43.5 | 16.6 | 343 | 18.9% | 0.40 [-2.11, 2.91] | |
| Staffen U. Thorsen 2017-CNGB-First trimester | 51.6 | 23.1 | 270 | 54.8 | 21.2 | 270 | 16.7% | -3.27 [-6.34, -0.20] | |
| Staffen U. Thorsen 2017-CNGB-Second trimester | 60.4 | 28.2 | 270 | 60.8 | 20.3 | 270 | 14.5% | -3.33 [-6.97, 3.31] | |
| Staffen U. Thorsen 2017-Molla-Second trimester | 58.2 | 26.4 | 189 | 58.3 | 24 | 257 | 12.5% | 0.22 [-4.07, 4.51] | |

Total (95% CI) 1520 | 3768 100.0% | -2.54 [-4.65, -0.44] |

**Heterogeneity:** $\tau^2 = 4.49; \chi^2 = 14.57, df = 7 (P = 0.04); I^2 = 52%$

**Test for overall effect:** $Z = 2.37 (P = 0.02)$

#### B

| Study or Subgroup | Case | Control | Mean Difference | Mean Difference |
|-------------------|------|---------|-----------------|-----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Ingvid M. Sorensen 2012 | 65.8 | 26.5 | 109 | 73.1 | 27.2 | 219 | 16.5% | -7.30 [-13.44, -1.16] | |
| Ingvid M. Sorensen 2016-First trimester | 57.9 | 18.8 | 113 | 62 | 19.1 | 220 | 21.9% | -4.10 [-8.39, 0.19] | |
| Ingvid M. Sorensen 2016-Second trimester | 65.6 | 24.2 | 113 | 68.4 | 24.4 | 220 | 18.3% | -2.80 [-8.30, 2.70] | |
| Ingvid M. Sorensen 2016-Third trimester | 65.9 | 28.5 | 113 | 75 | 27.9 | 220 | 15.8% | -9.10 [-15.52, -2.68] | |
| Mattinen 2012 | 43.9 | 16.9 | 343 | 43.5 | 16.6 | 343 | 27.5% | 0.40 [-2.11, 2.91] | |

Total (95% CI) 791 | 1222 100.0% | -3.95 [-7.56, -0.33] |

**Heterogeneity:** $\tau^2 = 10.75; \chi^2 = 12.02, df = 4 (P = 0.02); I^2 = 67%$

**Test for overall effect:** $Z = 2.14 (P = 0.03)$

#### C

| Study or Subgroup | Case | Control | Mean Difference | Mean Difference |
|-------------------|------|---------|-----------------|-----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Ingvid M. Sorensen 2016-First trimester | 57.9 | 18.8 | 113 | 62 | 19.1 | 220 | 33.8% | -4.10 [-8.39, 0.19] | |
| Staffen U. Thorsen 2017-CNGB-First trimester | 51.5 | 23.1 | 270 | 54.8 | 21.2 | 270 | 66.2% | -3.27 [-6.34, -0.20] | |

Total (95% CI) 383 | 1205 100.0% | -3.55 [-6.05, -1.06] |

**Heterogeneity:** $\chi^2 = 0.10, df = 1 (P = 0.76); I^2 = 0%$

**Test for overall effect:** $Z = 2.79 (P = 0.005)$

#### D

| Study or Subgroup | Case | Control | Mean Difference | Mean Difference |
|-------------------|------|---------|-----------------|-----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Ingvid M. Sorensen 2016-Second trimester | 65.6 | 24.2 | 113 | 68.4 | 24.4 | 220 | 20.3% | -2.80 [-8.30, 2.70] | |
| Staffen U. Thorsen 2017-CNGB-Second trimester | 60.4 | 28.2 | 270 | 60.8 | 20.3 | 270 | 46.3% | -0.33 [-3.97, 3.31] | |
| Staffen U. Thorsen 2017-Molla-Second trimester | 58.2 | 26.4 | 189 | 58.3 | 24 | 257 | 33.4% | 0.22 [-4.07, 4.51] | |

Total (95% CI) 572 | 1781 100.0% | -0.65 [-3.13, 1.83] |

**Heterogeneity:** $\chi^2 = 0.77, df = 2 (P = 0.68); I^2 = 0%$

**Test for overall effect:** $Z = 0.51 (P = 0.61)$

#### E

| Study or Subgroup | Case | Control | Mean Difference | Mean Difference |
|-------------------|------|---------|-----------------|-----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Staffen U. Thorsen 2017-CNGB-Second trimester | 60.4 | 28.2 | 270 | 60.8 | 20.3 | 270 | 58.1% | -0.33 [3.97, 3.31] | |
| Staffen U. Thorsen 2017-Molla-Second trimester | 65.7 | 26.4 | 189 | 58.3 | 24 | 257 | 41.9% | 0.22 [-4.07, 4.51] | |

Total (95% CI) 459 | 1561 100.0% | -0.10 [-2.87, 2.68] |

**Heterogeneity:** $\chi^2 = 0.04, df = 1 (P = 0.85); I^2 = 0%$

**Test for overall effect:** $Z = 0.07 (P = 0.94)$
Based on overall analysis, Begg’s and Egger’s tests all indicated significant publication bias among the included studies in this meta-analysis (Begg’s test: \( p = 0.035 \), Egger’s test: \( p = 0.040 \)). Thus, trim and fill method was performed and showed no change of results, indicating good stability of the results in this meta-analysis.

**DISCUSSION**

The overall results of this meta-analysis indicated that maternal 25(OH)D levels during pregnancy is a risk factor of type 1 diabetes in offspring. However, the subgroup analyses by gestational trimester showed there was no association between maternal 25(OH)D levels in first or second gestational trimester and risk of type 1 diabetes in offspring. Among these included studies, only the study of Sorensen et al. (13) was not analyzed in the subgroup analyses by gestational trimester. In that study of Sorensen et al. (13), the samples were mainly from the last trimester. Moreover, the results in the study of Sorensen et al. (13) showed significantly association between maternal 25(OH)D levels during pregnancy and risk of type 1 diabetes in offspring. Moreover, in the study of Sorensen et al. (12), a significant and negative association of maternal 25(OH)D levels with risk of type 1 diabetes was found in third trimester, but not in first and second trimester. Thus, we can speculate that the risk of type 1 diabetes in offspring may be associated maternal 25(OH)D levels during late stages of pregnancy, but not early stages of pregnancy. Thus, gestational trimester may be a factor...
influencing the results of this meta-analysis.

Differently from the study of Miettinen et al. (15) which showed no difference in serum 25(OH)D concentration during first trimester of pregnancy between cases (mothers whose children later on developed type 1 diabetes) and controls (mothers had non-diabetic ‘healthy’ children), the studies performed by Sørensen et al. (12) and Thorsen et al. (16) showed that the lower 25(OH)D concentration during first trimester of pregnancy is associated with higher risk of type 1 diabetes in offspring. As known, the study of Miettinen et al. (15) was performed in Finland, the studies of Sørensen et al. (12) and Thorsen et al. (16) were performed in Norway. Thus, the region may be a factor resulting the difference. More studies should be performed to investigated it.

In addition, Miettinen et al. found the risk of type 1 diabetes in offspring may be associated maternal gene polymorphisms in the vitamin D related genes. Previous studies have showed that 25(OH)D levels can be mediated by genes of vitamin D metabolic enzymes, vitamin D-binding protein and vitamin D receptor (17–19). Based on the previous studies and the results of this meta-analyses (12, 14, 20), the maternal gene polymorphisms in the vitamin D related genes may influence the risk of type 1 diabetes in offspring through mediating the vitamin D metabolism. Thus, the genes polymorphisms in the vitamin D related genes may be also the factors resulting inconsistent results between studies. Maternal vitamin D status during early pregnancy is related with fetal and neonatal growth (21). Meanwhile, Novakovic et al. reported that maternal vitamin D predominated over genetic factors in determining neonatal circulating 25(OH)D concentrations (22, 23). Thus, the effect of maternal 25(OH)D levels during pregnancy on neonatal 25(OH)D concentrations may be one of the pathogenies of childhood type 1 diabetes. more studies should be performed to investigated it.

This is the first meta-analysis to evaluate the association between maternal 25(OH)D levels during pregnancy and risk of type 1 diabetes in offspring. However, some limitations of this meta-analysis should be noted. Firstly, only four studies were included and they were all conducted in Northern Europeans, the number of the included studies is too small and the results of the Northern Europeans are too biased, which may result in the instability of the results. Secondly, the significant heterogeneity was found. The subgroup analyses showed that gestational trimester may be one of the sources of heterogeneity and the results can be affected by it. Thirdly, although the trim and fill method indicated good stability of the results in this meta-analysis, the significant publication bias is nonnegligible. Furthermore, the regression analysis was performed in three included studies (Sørensen et al. (12, 13) and Thorsen et al. (16)). Among them, the two studies of Sørensen et al. (12, 13) provided positive outcomes of association between risk of childhood type 1 diabetes and maternal 25-hydroxyvitamin D levels during pregnancy. However, the Cox regression analysis in the study of Thorsen et al. (16) did not provide positive evidences. Moreover, the study of Miettinen et al. (15) did not perform the regression analysis and also obtained negative results. Thus, we performed this meta-analysis to comprehensively analyze it by using the data in these previous studies. Fortunately, the positive results were found in this meta-analysis. However, given the above limitations, more studies should be performed to further confirm the association between maternal 25(OH)D levels during pregnancy and risk of type 1 diabetes in offspring and explore the influence factors.

In conclusion, lower maternal 25(OH)D levels during pregnancy is associated with higher risk of type 1 diabetes in offspring. Gestational trimester may be a factor influencing the results of this meta-analysis.

Authorship
Research conception and design: XK; experiments: MZ and JC; statistical analysis of the data: YW; interpretation of the data: WT; writing of the manuscript: LC.

Disclosure of state of COI
The authors declared no conflict of interest.

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