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The joint role of thyroid function and iodine concentration on gestational diabetes risk in a population-based study

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Conflicts of interest

The authors have no conflicts of interest to declare.

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ABSTRACT

Introduction: Iodine is essential for thyroid function, and iodine deficiency during pregnancy is common in Europe and the USA. However, no published studies have examined the role of iodine deficiency in the relationship between thyroid function and gestational diabetes mellitus (GDM). **Material and methods**: We conducted a population-based, nested case-control study within the Finnish Maternity Cohort using pregnancy and perinatal outcome data from the Finnish Maternal Birth Register. We randomly selected 224 GDM cases with singleton pregnancies and 224 controls without GDM from all singleton births occurring in Finland during 2012-2013. Blood was drawn at 10-14 weeks' gestation and analyzed for serum iodide, thyroglobulin, and thyroid-stimulating hormone (TSH) concentrations. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) of GDM. **Results**: Very high thyroglobulin concentration (>95% percentile; >83 µg/L) was not associated with significantly altered odds of GDM compared to those with normal levels (OR 0.41; 95%CI: 0.12, 1.38). High concentrations of TSH were also not associated with increased odds of GDM compared to normal levels of TSH (OR 0.45; 95% CI: 0.06, 3.18). Women in the lowest 5th percentile (<1.58 ng/mL) of iodine did not have increased odds of GDM compared to those with iodide in the highest quartile (OR 0.39; 95% CI: 0.11, 1.35). **Conclusions**: Low levels of iodide and thyroid function in early pregnancy are not associated with increased risk of GDM in this mildly iodine-deficient population.

Keywords

thyroid, iodine, gestational diabetes, diabetes, thyroid-stimulating hormone, thyroglobulin

Abbreviations

Tg thyroglobulin

TSH thyroid-stimulating hormone

GDM gestational diabetes mellitus

FMC Finnish Maternity Cohort

OR odds ratio

CI confidence interval

Key message

Abnormal thyroid function and iodine deficiency have been suggested to play a role in risk of gestational diabetes mellitus. Our population-based case-control study found no evidence of association between serum iodide, thyroglobulin, thyroid-stimulating hormone, and gestational diabetes mellitus.

INTRODUCTION

Gestational diabetes mellitus (GDM) has critical short and long-term health implications for both mothers and children. As Western populations shift to more sedentary lifestyles, increasing numbers of women are entering pregnancy overweight or obese and insulin resistant, which increases rates of GDM [1]. Thyroid hormones are involved in glucose metabolism and insulin sensitivity, and thyroid disease and diabetes are common comorbid conditions [2]. Only a few studies have examined the relationship between thyroid function and development of GDM, and these have produced mixed results [3-8]. More data are needed to characterize how thyroid function may affect GDM risks.

Iodine is essential for healthy thyroid function, and iodine deficiency has been recognized as an important health problem in the USA and parts of Europe (including Finland) [9]. Pregnant women have higher iodine requirements than non-pregnant women, and are more likely to be iodine deficient than non-pregnant women [9]. Iodine status and thyroid function play an important role in metabolic function. However, no published studies have examined the potential role of iodine deficiency in the relationship between thyroid function and GDM, nor are there reports of iodine concentrations and pregnancy outcomes in Finnish women [2, 10-12]. The main objective of our study is to explore the relationship between thyroid hormones, iodine concentrations, and risk of GDM in Finnish women.

MATERIAL AND METHODS

We conducted a population-based, nested case-control study within the Finnish Maternity Cohort (FMC) with pregnancy and perinatal outcome data from the Finnish Maternal Birth Register. Since 1983, the FMC has collected approximately 2 million serum samples from more than 950,000 women in Finland, comprising over 98% of pregnant Finnish women. Blood samples were collected by Maternity Care Units near the end of the first trimester (generally between 10-14 weeks) as part of routine prenatal care for screening for HIV, syphilis, and hepatitis B. One maternal serum sample was obtained for each pregnancy. Samples were then processed and stored at -25° C. Using a unique personal identification number (PIN), which has been assigned to each resident of Finland since 1971, FMC data were linked to the Finnish Maternal Birth Register, which contains data on all livebirths and stillbirths in Finland. The Finnish Maternal Birth Register was used to identify cases of GDM and controls without GDM and provided demographic and data collected from medical records for each participant. Cases and controls were selected from singleton birth records in the Finnish Maternal Birth Register from 2012-2013. Cases are defined as having an abnormal 75 g 2-hour oral glucose tolerance test. In all, 200 cases of GDM with serum available were identified for this study. Controls (N=250) were selected from a random sample of records (without regard to disease status) from the same time window. Those who were selected as controls but were found to have a diagnosis of GDM were moved to the case group (N=24), leaving 224 cases and 226 controls for analysis. After excluding two women with pre-existing diabetes from the controls, the final number of controls was 224.

A detailed description of the iodide assay can be found in the Supporting Information Appendix S1. Briefly, after serum samples were thawed at room temperature and vortex mixed for 30 seconds, 200 µL were transferred to polypropylenes tubes. Samples were pretreated, centrifuged, and analyzed by high performance liquid chromatography (Alliance 2695 HPLC) coupled with electrospray triple quadrupole mass spectrometry (Micromass, ESI-MS/MS; Waters Corporation, Milford, MA). Identification and quantification of ^{18}O -labeled-perchlorate, ^{13}C-labeled-thiocyanate, and iodide was performed using electrospray negative ionization (ESI-) and multiple reaction monitoring. Thyroglobulin (Tg) is a precursor of thyroid hormones that is elevated in the presence of iodine deficiency, and thyroid-stimulating hormone (TSH) is a pituitary hormone that regulates endocrine function in the thyroid and is an important indicator of thyroid function and metabolism [13]. Both serum Tg and serum TSH concentrations were measured using a commercial immunoassay (Siemens Immulite and Siemens Advia Centaur, respectively) (Siemens AG, Munich, Germany). The intra- and interassay coefficients of variation for Tg were <8% and <12%, respectively, and for TSH <5% and <5%, respectively. The analyzing laboratory performs daily quality control checks using commercial material and participates in external quality control. The TSH method is accredited according to the ISO 15189 standard. Data on women whose hypothyroidism was treated or resolved prior to pregnancy were not available.

Statistical Analyses

Distributions of variables between case and control groups were compared using descriptive statistics and statistical tests for normality. Parametric or nonparametric Mann-Whitney U and chi-square tests were performed to examine differences as appropriate, depending on whether data were normally distributed. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for GDM by increasing concentration of iodide, Tg and TSH. High, normal, low and very low iodide were defined as >75th percentile, 25-75th percentile, <25th percentile and < 5th percentile of the distribution in the control population, respectively. Tg concentrations were categorized as very high (>95th percentile in the control population, >83.6 µg/L) and high (>75th percentile, >35 µg/L) in the control population. Women were categorized as having low TSH if their TSH concentration was below previously defined reference intervals in pregnancy (<0.1 and <0.2 mU/L in the first and second trimester, respectively) and high TSH if their TSH concentration was over the

reference interval (>3.1 and >3.5 mU/L in the first and second trimester, respectively) [14]. All models were first run unadjusted and further adjusted for maternal age, maternal body mass index, smoking during pregnancy, parity, marital status, and socio-economic status (based on national classifications on occupations and their socio-economic status). Adjustment variables were chosen a priori based on scientific literature review. P values were considered significant at the alpha < 0.05 level. Analyses were performed using SAS 9.4 (SAS Institute, Cary NC, USA).

Ethical Approval

Mothers in the FMC provided informed written consent for their samples and data to be used for research purposes. This study was approved by the steering committee of the FMC, the ethics committee of the Northern Ostrobothnia Hospital District, Oulu, Finland, and the National Institutes of Health Office of Human Research Protections, Bethesda, MD, United States (#13459).

RESULTS

Women with GDM were older (median of 31.0 years compared to 29.0 years) and had higher body mass index (median of 26.7 compared to 23.5) than women without GDM (Table 1). Cases of GDM and controls had similar smoking status (18.3% of women with GDM, 14.6% of non-GDM women), marital status (93.8% of women with GDM were married or cohabitating, 88.0% of non-GDM women), and prevalence of preeclampsia (GDM 4.0%, non-GDM 1.3%). Cases and controls were at similar gestational ages at the time of blood draw. Median iodide in cases was 21.69 ng/mL (range 0.70 to 181.10 ng/mL), while median iodide in controls was 18.38 ng/mL (range 0.10 to 142.24 ng/mL). In cases, median Tg was 18.70 µg/L (range 0.20 to 192.00 µg/L), compared to 23.10 µg/L (range 0.25 to 251.00 µg/L) in controls. Median TSH in cases was 0.99 mU/L (range 0.01 to 4.88 mU/L), while median TSH in controls was 1.14 mU/L (range 0.10 to 5.00 mU/L).

After adjustment for age, body mass index, socio-economic status, smoking, parity and marital status, we observed no association with odds of GDM among those in the lowest quartile of iodide concentration compared to those in the highest quartile (OR 0.57; 95% CI: 0.32, 1.04), nor among those in the lowest 5th percentile of iodide (OR 0.39; 95% CI: 0.11, 1.32) (Table 2). Results were similar when comparing the lowest quartile of iodide concentration to the 25th to 75th quartiles (OR 0.74; 95% CI: 0.43, 1.29). Pregnant women in the highest quartile of Tg were not at significantly different odds of GDM compared to those with normal Tg levels (OR 0.75; 95% CI: 0.45, 1.23). Having very high Tg (>95% percentile) was not associated with significantly altered odds of GDM compared to those with lower levels (OR 0.41; 95% CI: 0.12, 1.38). High levels of TSH were also not associated with increased odds of GDM compared to normal levels of TSH (OR 0.45; 95% CI: 0.06, 3.18). When restricting analyses to only pregnant women with normal TSH, results for iodine and Tg remained similar (data not shown).

DISCUSSION

In our large, prospective, nested case-control study, we found that thyroid function and iodine concentration in early pregnancy was not associated with increased risk of GDM. We observed that higher Tg concentrations (which are generally higher in populations with iodine insufficiency) were not associated with GDM, nor were elevated concentrations of TSH. We also found that low serum iodide was not associated with risk of GDM in this representative population, which was generally euthyroid, with Tg and TSH mostly within the normal range, and with only mild levels of iodine insufficiency. Ours is the first study to prospectively examine thyroid function and risk of GDM using serum iodide as a factor. From these results, it seems unlikely that iodine deficiency-related thyroid dysfunction plays an important role in recent increases in rates of GDM in developed countries with mild iodine deficiency.

Thyroid conditions have been linked to GDM in some studies, however overall results have been mixed. A meta-analysis reported that risk of GDM was higher in pregnant women with subclinical hypothyroidism compared to euthyroid pregnant women; however, this finding was not significant after sensitivity analyses [3]. Männistö et al. 2013 found that women with primary hypothyroidism were at increased risk for GDM (OR 1.57 (95% CI: 1.33-1.86) in the Consortium on Safe Labor, a retrospective cohort study [4]. Karakosta et al.

found elevated TSH >2.53 mU/L was associated with increased risk of GDM [6]. In contrast, Yang et al. found higher levels of TSH >1.36 mU/L were associated with reduced risk of GDM [15]. In the Fremantle Diabetes Study, Kapadia et al. also found that higher levels of TSH were associated with insulin sensitivity [2]. Some studies of treatment for hypothyroidism in pregnancy have reported associations with GDM, however other studies have found no association [16-18]. Our study sample of healthy euthyroid women had low levels of TSH which were all essentially within the normal range. In vivo and in vitro studies have shown associations between hypothyroidism and insulin resistance, however these have been reported at more severe levels of thyroid dysfunction [11, 12].

We are aware of only one prior study that directly assesses the association between iodine levels in early pregnancy and GDM [19]. Charoenratana et al. found an association approaching significance (RR 1.79; 95% CI 0.95-3.37) among women in Thailand. However, women included in that study had high levels of iodine insufficiency compared to those among Finnish women [20]. Varying levels of underlying iodine insufficiency between the two populations, as well as differences in race, genetics, thyroid function, environmental factors, and geographic area, make comparison between the studies difficult. Participants in the Charoenratana et al. study were only selected if they were not taking iodine supplements, while subjects in our study were a random sample of pregnant women and likely included women who used supplements containing iodine. A recent study examining the effects of iodine on thyroid function observed a U-shaped relationship between iodine concentration and Tg, where both very low and very high levels of iodine associated with high Tg [13]. The women in our representative sample were predominantly euthyroid, occupying the bottom curve of the U-shape, which may explain our observed associations between iodide and reduced risk of GDM [13]. The mechanisms explaining the relationship between higher levels of iodine and increased Tg remain to be explored. Higher Tg levels may be related to the Wolff-Chaikoff effect, in which iodine inhibits the thyroid from synthesizing thyroid hormone, resulting in higher levels of Tg and TSH [21]. Other studies have also shown low correlations between iodine and TSH among pregnant women [22-24]. It is likely that only severe iodine deficiency would affect TSH excretion, as the thyroid becomes unable to produce T4 or T3 and low circulating hormones lead to TSH elevation.

Our study had a number of strengths. Data on exposures, outcomes, and confounders were collected prospectively. Cases and controls were selected at random from national administrative records covering the entire population of pregnant Finnish women, thus

reducing risk of selection bias. While most studies of iodine status have used urinary iodine concentrations - which are susceptible to high day-to-day variability from recent dietary intake and urine dilution - our study used a novel measurement of iodide concentrations in serum, reducing the shorter-term variability common in most urinary biomarkers [25]. Diagnoses of GDM were made by physicians according to standardized guidelines. Our study also had several limitations. Data were not available on whether pregnant women took iodine-containing supplements after blood samples were taken. If iodine levels at later periods of gestation are more relevant to risk of GDM, this would hinder our ability to detect an association. Further study of iodine status at later stages of pregnancy are necessary to confirm our findings. Data were also unavailable on possible treatments for hypothyroidism prior to pregnancy, however recent trials of treatment for subclinical hypothyroidism showed no effect on GDM [26]. Detailed data on smoking was unavailable, so there may be some misclassification of smoking status. The thyroid system is quite complex, and complete assessment of thyroid function is difficult from a limited number of individual thyroid measures, particularly in a population undergoing physiological changes due to pregnancy. Although we accounted for multiple confounding factors associated with iodine status, thyroid function, and GDM, there may be unmeasured confounders that could bias our estimates. Most confounders did not strongly differ between cases and controls, however, and adjustment for confounders did not change the estimates of effect greatly. Power calculations assuming a 15% prevalence of mild iodine deficiency among cases and a 1:1 ratio of cases and controls, showed that a sample size of 200 women per group would be sufficient to detect a 10% difference in prevalence of iodine deficiency between cases and controls with >80% power. Our study examined numerous comparisons, and the associations that achieved statistical significance at the $p<0.05$ level were not significant after accounting for multiple testing.

CONCLUSION

Our study provides reassuring new evidence that low levels of iodide are not associated with increased odds of GDM in this population of pregnant Finnish women. In other Nordic countries once thought to be iodine sufficient, there is growing evidence that changing dietary patterns are increasing the prevalence of iodine deficiency, making surveillance of iodine status and thyroid function in populations known to be mildly iodine

deficient, such as Finland, of crucial importance [20, 24, 27-29]. The most common sources of iodine in the Finnish diet are from dairy products (from voluntarily fortified feed) and iodized salt; however, consumption of both dairy and salt in the country have declined over the past decade [20]. Characterization of the potential risks of mild iodine deficiency is also crucial for estimating possible health gains from improved iodine supplementation policies [30]. While numerous studies have examined the effects of iodine deficiency on birth outcomes in offspring, few studies have explored associations between mild iodine deficiency, its relationship with thyroid function, and GDM. Our study is the first to explore the relationship between these metabolically linked factors, and the first to report on iodine status and GDM in this population. In future studies, both iodine concentrations and iodine supplement intake should be examined longitudinally throughout the gestational period to confirm these findings.

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Supporting Information legend:

Appendix S1. Iodine measurement

Table 1. Maternal characteristics according to gestational diabetes mellitus (GDM) status, among 448 mothers in the Finnish Maternity Cohort, 2012-2013

Demographics	GDM (N=224)	Controls (N=224)	P-value[†]
Median age, years (min-max, IQR)	31.0 (20-44, 7.0)	29.0 (18-48, 8.0)	<0.001
Median BMI, kg/m^2 (min-max, IQR)*	26.7 (18.0-55.8, 7.8)	23.5 (15.9-39.9, 4.8)	<0.001
Smoking status, No. (%)			
Nonsmoker	180 (80.4)	187 (83.5)	0.565
Smoker	41 (18.3)	33 (14.6)	
Unknown	3 (1.3)	4 (1.8)	
Socioeconomic status, No. (%)			
Blue-collar worker	28 (12.5)	28 (12.5)	0.336
Lower white-collar worker	74 (33.0)	58 (25.9)	
Upper white-collar worker	33 (14.7)	26 (11.6)	
Entrepreneur or farmer	8 (3.6)	8 (3.4)	
Student	15 (6.7)	21 (9.3)	
Other/Unknown	66 (29.5)	83 (37.1)	
Diagnosed thyroid disease, No. (%)	4 (1.8)	0 (0)	0.123
Maternal conditions, No. (%)			
Chronic hypertension	4 (1.8)	2 (0.9)	0.685
Preeclampsia	9 (4.0)	3 (1.3)	0.079
Gestational hypertension	8 (3.6)	5 (2.2)	0.575
Marital status, No. (%)			
Married or cohabiting	210 (93.8)	197 (88.0)	0.093
Single, separated, or widowed	13 (5.8)	26 (11.6)	
Unknown	1 (0.5)	1 (0.4)	
Median gravidity, median (min-max,	1.0 (0-11, 2.0)	1.0 (0-12, 2.0)	0.012

IQR)			
Median parity, median (min-max, IQR)	1.0 (0-10, 2.0)	1.0 (0-12, 1.0)	0.214
Nulliparous, No. (%)	88 (39.3)	100 (44.6)	0.292
Median gestational age at screening (weeks) (min-max, IQR)	10.3 (6.0-29.1, 1.9)	10.4 (5.7-28.1, 2.3)	0.557
Median gestational age at birth, weeks (min-max, IQR)	39 (31-42, 2.0)	40 (29-42, 1.0)	0.002
Median TSH, IU/l (min-max, IQR)**	0.99 (0.01-4.88, 0.95)	1.23 (0.01-5.00, 1.01)	0.127
Median Tg, µg/l (min-max, IQR)**	18.70 (0.20-192.00, 19.60)	23.10 (0.25-251.00, 22.10)	0.027
Median iodide, ng/ml (min-max, IQR)	21.69 (0.70-181.10, 37.40)	18.38 (0.10-142.24, 31.24)	0.073

† Mann-Whitney U tests were used to test differences in continuous variables, while chi-squares were used to test differences in counts.

* Data are missing for 4 cases and 2 controls. **Data are missing for 3 controls

IQR, interquartile range; BMI, body mass index.

Table 2. Associations of maternal serum iodide, thyroglobulin, and thyroid-stimulating hormone exposures with gestational diabetes mellitus (GDM) in the Finnish Maternity Cohort, 2012-2013 (controls N=224 ; GDM N=224)

	Unadjusted			Adjusted for age, BMI, SES, smoking, parity, marital status		
	Odds Ratio	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
Continuous iodide, 5 ng/ml unit increase	1.023	0.991-1.056	0.160	1.017	0.982-1.054	0.350
Lowest quartile of iodide compared to 25th-75th percentile	0.649	0.396-1.064	0.086	0.746	0.430-1.292	0.295
Highest quartile of iodide compared to 25th-75th percentile	1.310	0.849-2.021	0.223	1.298	0.805-2.094	0.285
Lowest quartile of iodide compared to highest quartile	0.495	0.287-0.854	0.003	0.574	0.316-1.044	0.153
Very low iodide (<5th percentile), compared to $\geq 5^{th}$ percentile	0.442	0.151-1.294	0.136	0.387	0.111-1.346	0.136
Low iodine, high Tg vs. normal iodide, normal Tg	0.267	0.084-0.842	0.024	0.397	0.119-1.324	0.133
Low iodide, normal Tg vs. normal iodide, normal Tg	0.728	0.420-1.262	0.259	0.736	0.399-1.359	0.327
High Tg, normal iodide vs. normal iodide, normal Tg	0.830	0.444-1.550	0.558	0.611	0.295-1.262	0.183

High Tg, High iodide vs. normal iodide, normal Tg	1.120	0.531-2.364	0.766	1.159	0.516-2.601	0.721
High iodide, normal Tg vs. normal iodide, normal Tg	1.307	0.790-2.161	0.297	1.177	0.674-2.055	0.567
Continuous Tg, 5 ng/ml unit increase	0.971	0.937-1.006	0.099	0.962	0.926-0.999	0.047
Highest quartile of Tg vs. <75th percentile	0.775	0.498-1.208	0.261	0.746	0.453-1.228	0.249
Very high Tg (over 95th percentile) vs. <95th percentile	0.442	0.151-1.294	0.136	0.410	0.121-1.384	0.151
Continuous TSH, one mIU/l increase	0.781	0.611-0.999	0.049	0.688	0.519-0.913	0.010
Low TSH vs. normal TSH	1.170	0.512-2.673	0.709	1.253	0.502-3.125	0.629
High TSH vs. normal TSH	0.396	0.076-2.066	0.272	0.446	0.063-3.176	0.420

Abbreviations: Thyrogobulin (Tg), thyroid stimulating hormone (TSH), body mass index (BMI), socio-economic status (SES)